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(71) Applicant *(for all designated States except US)*: THE SALK INSTITUTE BIOTECHNOLOGY/INDUSTRIAL ASSOCIATES, INC. [US/US]; Suite 300, 505 Coast Boulevard South, La Jolla, CA 92037 (US).

(71)(72) Applicants and Inventors: MUNOZ, Benito [CA/US]; 6977 Schilling Avenue, San Diego, CA 92126 (US). MCDONALD, Ian, Alexander [AU/US]; 4722 Shadwell Place, San Diego, CA 92130 (US). ALBRECHT, Elisabeth [US/US]; 10540 Bannister Way, San Diego, CA 92126 (US).

(74) Agent: SEIDMAN, Stephanie; Brown, Martin, Haller & McClain, 1660 Union Street, San Diego, CA 92101-2926 (US).

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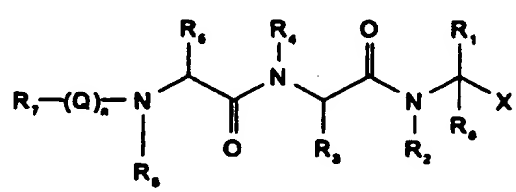
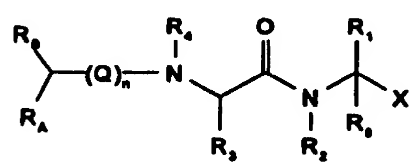
(54) Title: PEPTIDE, PEPTIDE ANALOG AND AMINO ACID ANALOG PROTEASE INHIBITORS

(57) Abstract

Methods of use of compounds and compounds for the treatment of disorders characterized by the cerebral deposition of amyloid are provided. Among the compounds are those of formulae (I), (II) and (III), in which R_1 is preferably 2-methyl propene, 2-butene, norleucine; R_2, R_4, and R_8 are each independently methyl or ethyl; R_3 is preferably *iso*-butyl or phenyl; R_5 is preferably *iso*-butyl; R_6 is H or methyl; R_7 - $(Q)_n$ is preferably benzyloxycarbonyl or acetyl; Q is preferably -C(O)-; R_B is preferably *iso*-butyl; R_A = $-(T)_m-(D)_m-R_1$, in which T is preferably oxygen or carbon, and D is preferably a mono-unsaturated C_{3-4} alkenyl; and X is an alcohol, particularly a secondary alcohol.



(I)



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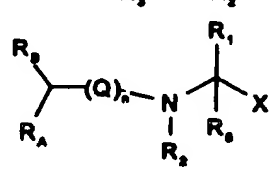

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PEPTIDE, PEPTIDE ANALOG AND AMINO ACID ANALOG PROTEASE INHIBITORS

This application is a continuation-in-part of U.S. application Serial No. 08/403,420 to Munoz et al., filed March 13, 1995, entitled *PEPTIDE, PEPTIDE ANALOG AND AMINO ACID ANALOG PROTEASE INHIBITORS*. This application is also a continuation-in-part of U.S. application Serial No. 08/369,422 to McDonald et al., filed January 6, 1995, entitled *PEPTIDE AND PEPTIDE ANALOG PROTEASE INHIBITORS*. U.S. application Serial No. 08/403,420 is a continuation-in-part of U.S. Patent No. 08/369,422. The subject matter of each of U.S. application Serial No. 08/369,422 and U.S. application Serial No. 08/403,420 is herein incorporated in its entirety by reference.

FIELD OF THE INVENTION

This invention relates to peptidyl compounds useful for a variety of physiological end-use applications. More specifically, peptide and amino acid analogs that are protease inhibitors are provided. These inhibitors are useful in the treatment of certain diseases, including neurodegenerative diseases characterized by the accumulation of amyloid plaques, and in diseases characterized by degeneration of the neuronal cytoskeleton.

BACKGROUND OF INVENTION

Proteases play a key role in metabolism and in the pathology of numerous disorders. As a consequence, compounds that specifically inhibit protease activity are often therapeutic. For example, renin is an aspartyl protease that cleaves angiotensinogen to angiotensin I. Angiotensin I is hydrolyzed by angiotensin converting enzyme (ACE) to angiotensin II, which is a potent vasoconstrictor and stimulant of aldosterone secretion. Compounds that inhibit the activity of ACE, such as captopril an orally active ACE inhibitor, are therapeutically effective for treating hypertension and congestive heart failure. Renin inhibitors are thought to have similarly beneficial therapeutic activity.

Activated ketone-based inhibitors have found uses as inhibitors of four different classes of proteases, serine proteases, aspartyl proteases, cysteine proteases and metalloproteases, because they exist as hydrates in aqueous media and directly serve as transition state analogs and/or react with a nucleophilic residue (such as the serine hydroxyl or cysteine sulfhydryl) to form a reversible hemiacetal-type intermediate. For example, phenylalkyl ketones are potent and competitive reversible inhibitors of interleukin 1-β converting enzyme (ICE) and thus, are thought to have therapeutic use for treatment of certain chronic inflammatory disease states. The precursor alcohols for these ketones have been reported to have substantially reduced protease activity compared to the corresponding ketone [see, e.g., Patel et al. (1988) Tetrahed. Lttrs. 29:4665-4668; Patel et al. (1993) J. Med. Chem. 36:24310-2447].

Trifluoromethyl ketones are inhibitors of, for example, human leukocyte elastase (HLE), which is a serine protease. This enzyme has been implicated as a pathogenic agent in a variety of disorders, including pulmonary emphysema, rheumatoid arthritis, adult respiratory distress syndrome (ARDS), glomerulonephritis and cystic fibrosis [see, e.g., Skiles et al. (1992) J. Med. Chem. 35:641-662; Angelastro et al. (1994) J. Med. Chem. 37:4538-4554].

Proteases are also implicated in diseases, such as Alzheimer's Disease (AD), that are characterized by the accumulation of amyloid plaques. Amyloidogenic Aβ peptides (Aβ) are the principle component of the amyloid plaques that accumulate intracellularly and extracellularly in the neuritic plaques in the brain in AD. Aβ is an ~4.0 kDa protein, about 39-43 amino acids long, that is derived from a C-terminal region of amyloid precursor protein (APP). APP is a membrane-spanning glycoprotein that, in one processing pathway, is cleaved inside the Aβ domain to produce α-sAPP, a nonamyloidogenic secreted form of APP. Formation of α-sAPP precludes formation of Aβ. It has been proposed

that $A\beta$ is generated by virtue of a different processing pathway, so that compounds that inhibit the activity of enzymes responsible for $A\beta$ production are being sought [see, e.g., Wagner et al. Biotech. Report (1994/1995), pp. 106-107; and Selkoe (1993) TINS 16:403-409].

Because proteases are implicated in numerous disorders, there is a need to develop potent and specific inhibitors of these enzymes. Therefore, it is an object herein to provide methods of treating disorders in which protease activity plays a pathological role. It is also an object herein to provide protease inhibitors.

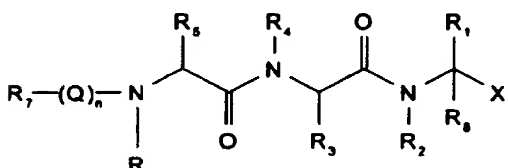
SUMMARY OF THE INVENTION

Methods of inhibiting proteases are provided. The protease inhibitors used in the methods are peptidyl, peptidyl analog and amino acid analog alcohols, particularly haloalkyl secondary alcohols. These inhibitors include the corresponding alcohols of any peptidyl or peptidyl analog ketones or aldehydes that inhibit proteases in cell-free assays [see, EP 0 410 411 A2, which is based on U.S. application Serial No. 07/385,624, WO 92/20357, which is based on U.S. application Serial No. 08/704,449, EP 0 364 344 A2, which is based on U.S. application Serial No. 08/254,762] as well as compounds particularly provided herein. Peptidyl, peptidyl analog and amino acid analog alcohol protease inhibitors that do not correspond to such known ketone or aldehyde inhibitors are also provided herein.

Thus, di- and tri-peptide analogs and amino acid analogs and methods of treating certain disorders, particularly cognitive disorders, but any disorder in which a protease, particularly a serine, cysteine or aspartyl protease, is involved in the pathology, and methods of inhibiting proteases using the compounds are provided. Among the compounds used in the methods are peptidyl or peptidyl analog haloalkyl alcohols, particularly secondary alcohols and fluoro-lower-alkyl alcohols.

Methods of identifying and isolating proteases are provided herein. Also provided are methods of identifying protease inhibitors.

In particular, the methods, particularly the methods for treating cognitive disorders involving accumulation of amyloid plaques in the brain tissue, use compounds having formulae:



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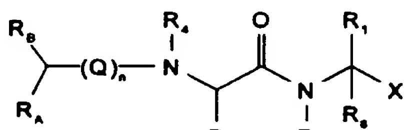

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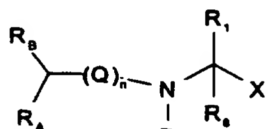
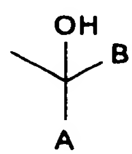


III

or the hydrates and isosteres, diastereomeric isomers and mixtures thereof, or pharmaceutically acceptable salts thereof.

X has the formula:



where A and B are independently selected from among H, halogen, alkyl, heterocycle, arylalkyl, haloalkyl, in which the alkyl groups are straight or branched chains or form a fused ring(s) or preferably a single ring, aryl, particularly halo-substituted aryl, alkylhaloaryl, $(CH_2)_rCHN_2$, $CH_2(CH_2)_rOR_D$, $CH_2(CH_2)_rOZ_D$, $-(CH_2)_{r+1}W$, $-(CH_2)_{r+1}U$ in which:

the carbon or heterocyclic ring(s) contain from 3 to about 20 members, preferably 5-7, in the ring(s), which are unsubstituted or are

substituted with one or more substituents independently selected from G;

the aryl, cyclic and heterocyclic portions of X can be further substituted with G;

r is 0-5, preferably 0-3, more preferably 0 or 1, most preferably 0;

G is halogen, preferably F, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR';

R and R' are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3;

the aryl groups preferably contain from 5-6 members and are unsubstituted or substituted with one or more substituents independently selected from G, which is preferably halogen, more preferably fluoro;

the heterocyclic rings preferably contain one or two heteroatoms and preferably contain 5 or 6 members;

Z_D is haloalkyl, in which the alkyl portion is straight or branched, cyclic, or mixtures thereof, the straight or branched chains contain from 1 to about 10, preferably 1-8, more preferably 1-6, most preferably 1-3, carbons in the chain, and the cyclic portions contain from 3 to about 10, preferably 3-7, carbons in the cycle, and the halo portion is preferably fluoro;

U is $-OR_D$ or $-NR_DR_E$;

R_D and R_E are independently selected from among H, alkyl, preferably lower alkyl, more preferably C_{1-4} alkyl, phenyl, and phenethyl;

W is $-OR_D$, $-SR_D$, and $-NR_DR_E$, or a heterocyclic moiety, such as a thiazolyl, preferably containing 4-6, more preferably 5 or 6 members in the ring, and preferably one or two heteroatoms, selected from O, S, or N, in the ring. Preferably, at least one of A or B is H.

In particular, X is selected from among $(CH_2)_{r+1}C(OH)$halo-substituted alkyl or CH(OH)halo-substituted alkyl, preferably $-CH(OH)C_kH_{(2k+1-s)}F_s$ in which k is 1-6, preferably 1-3, s is 0 to 2k+1; $-CH(OH)C_6H_{(5-q)}F_q$ in which q is 0 to 5; $-(CH_2)_{r+1}C(OH)CF_3$, $-CH(OH)CF_3$,

$-(CH_2)_{r+1}C(OH)C_2F_5$, $-CH(OH)C_2F_5$, $-(CH_2)_{r+1}C(OH)H$, -CH(OH)H, $-(CH_2)_{r+1}C(OH)(CH_2)_rCHN_2$, $-CH(OH)(CH_2)_rCHN_2$, $-(CH_2)_{r+1}C(OH)$haloalkyl, -CH(OH)haloalkyl, $-(CH_2)_{r+1}C(OH)(CH_2)_rU$, $-CH(OH)(CH_2)_rU$, $-(CH_2)_{r+1}C(OH)CH_2W$ and -CH(OH)haloaryl. X is more preferably $-CH(OH)CF_3$ or $-CH(OH)C_2F_5$. In all embodiments, halo is preferably fluoro.

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi) or (vii) as follows:

(i) R_1, R_3, R_5, and R_B, are each independently selected from a side chain of a naturally occurring α-amino acid, H, alkyl, preferably lower (C_{1-6}) alkyl, alkenyl, preferably C_{2-10} alkenyl, alkynyl, preferably C_{2-6} alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, Y-substituted aryl, aralkyl, aralkenyl, aralkynyl, and Z-substituted heteroaryl, heteroaralkyl, heteroaralkenyl, in which Y is selected from halogen, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR', R and R' are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3, Z is lower alkyl, preferably C_{1-4} alkyl, or halo lower alkyl, preferably C_{1-4} haloalkyl, more preferably CF_3;

R_2, R_4, R_6, and R_8 are each independently selected from among H and lower alkyl, preferably C_{1-4} alkyl;

R_7 is selected from among C_{1-6} alkyl, aryl, alkenyl, 9-fluoroenyl, aralkyl, aralkenyl, aralkynyl the aryl groups are unsubstituted or are substituted with Z;

Q is selected from among -C(O)-, -O-C(O)-, -C(O)O, $-S(O)_2$- and HN-C(O)-;

n is zero or one;

R_A is $-(T)_m-(D)_m-R_1$ in which T is O or NH, and D is C_{1-4} alkyl or C_{2-4} alkene; and m is zero or one; or

(ii) R_1, R_2, R_3, R_4, R_5, and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH;

n is zero; and

R_6 and R_7 are selected so that with the atoms to which each is attached they form a heterocyclic moiety, which:

(a) contains from 3 to 21 members and one or two or more fused rings, each ring containing preferably 3 to 7, more preferably 4 to 6, members, and is preferably morpholino, thiomorpholino, pyrrolidinyl, V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl, or a reduced isoquinoline, preferably 1,2,3,4,tetrahydroisoquinoline;

(b) does not contain adjacent heteroatoms;

(c) is unsubstituted or substituted with one or more substituents selected from Y, more preferably from V, and most preferably selected from among OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH; or

(iii) R_1, R_2, R_3, R_4, R_5 and R_8 are selected as in (i);

V is as defined in (ii);

Q is C(O);

n is one; and

R_6 and R_7 are each independently selected as follows:

(a) from carbonyl (C=O), phenyl, a heteroatom, lower alkyl, preferably C_{1-3} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-3} alkyl, and

(b) each is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a cyclic moiety, preferably a 4-6 membered cyclic or 8-12 membered bicylic moiety, and

(d) R_6 and R_7 are selected with the proviso that when two or more heteroatoms are present there is a carbon atom between the heteroatoms; and

(e) the cyclic moiety is preferably succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_B, Q and n are as defined in any of (i)-(iii) or (v)-(vii),

V is as defined in (ii);

R_8 is H; and

R_1 and R_2 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_1 and R_2 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, Q and n are as defined in any of (i)-(iv) or (vi)-(vii);

V is as defined in (ii);

R_3 and R_4 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom,

with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl;

(vi) R_1, R_2, R_3, R_4, R_7, R_8, Q and n are as defined in any of (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

R_5 and R_6 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_6 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6 and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

n is zero; and

R_5 and R_7 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_7 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl.

In all instances, unless specified, the carbon chains, which may be straight or branched or cyclic, contain from 1 to about 12 carbons preferably 1 to 6, and most preferably 4-6 carbons, and the cyclic moieties preferably contain one ring or two fused rings with from 3 to 16 atoms, preferably 4 to 12, with 4 to 6 in each ring, in the ring structures.

The compounds of formulae (I), (II) and (III) are particularly useful for the treatment of neurodegenerative disorders and other disorders involving the accumulation of amyloid plaques.

Unless otherwise stated, the α-amino acids or analogs thereof of the compounds of formulae I-III are preferably in their L-configuration. In their preferred configuration with reference to a particular compound, R_1 is *S*, R_3 is *S*, R_5 is *R/S*, and the chiral centers of X are *R/S*, *R*, *S* or any combination thereof, and are preferably *S*.

Also, a compound of these formulae may be in free form, e.g., an amphoteric form, or a salt form, e.g., an acid addition or an anionic salt. A compound may be converted to its salt or base form in an art-known manner, one from another. Preferred salts are trifluoracetate, hydrochloride, sodium, potassium or ammonium salts, although the scope

of the salts embraced is not limited thereto, the scope being extended to include all of those salts known to be used in the art of chemistry.

Compounds are also provided herein. These compounds may be used in the methods. In certain embodiments, the compounds have formulae (I) or (II), as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid and X is a tertiary or secondary haloalkyl alcohol, R_1 is not the side chain of cyclohexylalanine or cyclohexylglycine.

In other embodiments, when the compounds have formula (III), as defined above, when X is a tertiary or secondary haloalkyl alcohol, then R_1 is the side chain of a non-naturally-occurring α-amino acid and it is not the side chain of cyclohexylalanine or cyclohexylglycine.

In certain other embodiments, the compounds have formulae (I) or (II), as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, R_1 is not the side chain of cyclohexylalanine or cyclohexylglycine.

In certain other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): R_1 is a side chain of a non-naturally-occurring amino acid, the side chain of R_1 is of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, unless the compounds are primary alcohols, then the non-naturally-occurring amino acid is other than norleucine or norvaline.

In certain other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I), (II) or (III): R_1 is a side chain of a non-naturally-occurring amino acid, the side chain of R_1 is of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, unless the compounds are primary alcohols, then the non-naturally-occurring amino acid is other than norleucine or norvaline.

Thus, in certain other embodiments in which the compounds are primary alcohols, the compounds have formulae (I) or (II), particularly formula I, as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, it is not the side chain of norleucine or norvaline.

Thus, in certain other embodiments in which the compounds are primary alcohols, the compounds have formulae (I) or (II), particularly formula I, as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, it is not the side chain of cyclohexylalanine, cyclohexylglycine, norleucine or norvaline.

In other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine or norvaline.

In other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have

formula (I), (II) or (III): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine or norvaline.

In other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine, norvaline, citrulline, ornithine, 4-phenyl-2-aminobutyric acid, 1-naphthylalanine, 2-naphthylalanine, sarcosine, 2-indolinecarboxylic acid, *β*-alanine, *β*-valine, *N*-6-acetyllysine, O-4'-methyltyrosine, a substituted alanine and guanidinophenylalanine.

In other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I), (II) or (III): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine, norvaline, citrulline, ornithine, 4-phenyl-2-aminobutyric acid, 1-naphthylalanine, 2-naphthylalanine, sarcosine, 2-indolinecarboxylic acid, *β*-alanine, *β*-valine, *N*-6-acetyllysine, O-4'-methyltyrosine, a substituted alanine and guanidinophenylalanine.

In certain other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): at least one of the amino acid residues in the resulting di-peptide or tri-peptide is a non-naturally-occurring *α*-amino acid or at least one of the R_1, R_3 and R_5, preferably R_1, is a side chain of a non-naturally-occurring amino acid, R_1 is not cyclohexylalanine, and the at least one non-naturally-occurring amino acid (or side chain thereof) is other than norleucine or norvaline, unless the resulting residue is a halo-substituted alcohol, particularly fluoro-substituted alcohols. Such compounds include, but are not limited to: (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-

(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide and *N*-valeroyl-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide.

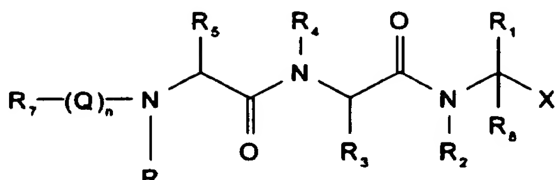
In other embodiments, the compounds have formulae (I) or (II) and at least one of R_1, R_3 and R_5, preferably R_1 or R_5, includes at least one unsaturated bond. Thus at least one of R_1, R_3 and R_5 is a straight or branched carbon chain containing at least one unsaturated bond, preferably a double bond, and 2 to 10, preferably 3 to 7, more preferably 4 to 6, carbon atoms in the chain. Such side chains include, but are not limited to substituted and unsubstituted propenes, butenes, pentenes, such as, 2-methyl-propenyl and 2-butenyl, which are among the preferred residues.

The compounds provided herein are preferred for use in the methods, particularly the methods of treatment of cognitive disorders.

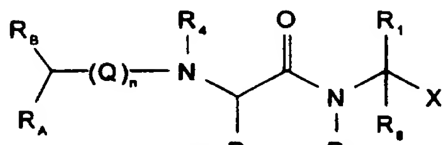
The compounds herein may be used in methods of identifying and classifying proteolytic enzymes.

Pharmaceutical compositions containing a compound of formulae (I), (II) or (III) are provided. In particular, pharmaceutical compositions formulated for single dosage administration are provided.

Combinations of compositions are also provided. The combinations contain: (A) a composition containing one or more compounds of formula (I), (II) or (III) set forth above; and (B) a composition containing compounds of copending U.S. application Serial No. 08/369,422, particularly of formula (IV) or (V):



IV



V

or the hydrates and isosteres, diastereomeric isomers and mixtures thereof, or pharmaceutically acceptable salts thereof, wherein:

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi) or (vii) as described above, X for the compounds of (B) is an aldehyde or ketone or preferably selected from among $-(CH_2)_rC(O)H$, $-(CH_2)_rC(O)$haloalkyl, $-(CH_2)_rC(O)(CH_2)_rCHN_2$, $-(CH_2)_rC{\equiv}N$, $-C(CH_2)_r(O)C(CH_2)_r(O)OR_D$, $-(CH_2)_rC(O)(CH_2)_rC(O)NR_DR_E$, $-(CH_2)_rC(OH)(CH_2)_rC(O)U$, $-(CH_2)_rC(OH)CH_2C(O)U$, $-(CH_2)_rC(O)W$ and $-(CH_2)_rC(O)CH_2W$; and U, W, and R_D, R_E, and r are as described above.

Methods of inhibiting proteases, particularly serine, cysteine, and aspartyl proteases, particularly intracellular proteases are provided. In particular, the proteases are responsible for cleavage of APP to produce $A\beta$.

Methods of treatment of diseases in which proteases play a pathological role are provided. Among these diseases are cognitive disorders, hypertension, inflammatory disorders and others. The methods are effected by administering an effective amount of the pharmaceutical compositions.

In particular, methods of treating a patient suffering from a neurodegenerative disease selected from among Alzheimer's disease, cognition deficits, Down's Syndrome, Parkinson's disease, cerebral hemorrhage with amyloidosis, dementia pugilistica, head trauma and any disorder characterized by an accumulation of plaques in the brain, by administering to the patient a therapeutically effective amount of a compound of formulae (I), (II) and (III) or compounds of formulae (I), (II) and (III) in which R_1, R_3, R_5 and R_8 can all be side chains of naturally-occurring amino acids are provided.

Methods of treating a patient suffering from a disease state characterized by the degeneration of the cytoskeleton arising from a thrombolytic or hemorrhagic stroke by administering a therapeutically effective amount of a compound provided herein are also provided.

Methods of inhibiting proteases and methods of treatment of disorders, particularly neurodegenerative disorders using the combinations in which (A) and (B) are used simultaneously, successively or intermittently are also provided.

Methods of identifying and classifying proteolytic enzymes are also provided. These methods are effected by measuring the activity of an enzyme in the presence and absence of a compound provided and ascertaining whether the enzyme activity is altered.

Methods are provided herein for identifying and/or isolating proteases. These methods use compounds having formulae (I) and (II) and (III) in which R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q, n and X are as defined above for formulae (I), (II) and (III), but in which either R_7-$(Q)_n$ in formula (I) and R_8-$CH(R_A)$-$(Q)_n$ in formulae (II) and (III) or X is replaced with a moiety, such as a chemical labeling/linker group or a chromophore or a fluorophore, useful for identifying and/or isolating proteases. For example in some embodiments, $(Q)_n$, R_7, R_A, and R_B are as defined above and X is replaced with a chromophore or fluorophore, preferably selected

from among p-nitroanilide, 4-methoxy-β-naphthylamide, or 7-amino-4-methylcoumarin. In other embodiments, X is as defined above and the R_7-$(Q)_n$ moiety and the (R_B)-$CH(R_A)$-$(Q)_n$ moiety are chemical labeling/linking groups that permit detection and/or isolation of the peptide to which they are coupled. These are preferably selected from among biotin, radiolabeled moieties, fluorescein, and primary amines such as 6-amino caproic acid and amino decanoic acid.

Also provided herein are methods of identifying protease inhibitors in *in vitro* competitive inhibition assays. These methods use compounds having formulae (I), (II) and (III) in which R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 R_A, R_B, Q and n are as defined above, but in which X is replaced with a chromophore or fluorphore, preferably selected from among p-nitroanilide, 4-methoxy-β-naphthylamide, or 7-amino-4-methylcoumarin. Such inhibitors may be useful in modulating the processing of amyloid precursor protein (APP).

Also provided herein are compounds having formulae (I), (II) and (III) in which R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q, n and X are as defined above for formulae (I), (II) and (III), but in which either R_7-$(Q)_n$ in formula (I) and R_B-$CH(R_A)$-$(Q)_n$ in formulae (II) and (III) or X is replaced with a moiety, such as a chemical labeling/linking group or a chromophore or a fluorphore, preferably selected from among p-nitroanilide, 4-methoxy-β-naphthylamide, or 7-amino-4-methylcoumarin. In certain of these embodiments, such compounds that include a chemical labeling/linking group or chromophore or fluorphore are as defined with the proviso that when these compounds have formulae (I) or (II): (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid and X is a tertiary or

secondary haloalkyl alcohol, R_1 is not the side chain of cyclohexylalanine or cyclohexylglycine.

In other of these embodiments, when such compounds that include a chemical labeling/linking group or chromophore or fluorphore have formula (III) and X is a tertiary or secondary haloalkyl alcohol, they are as defined with the proviso that: R_1 is the side chain of a non-naturally-occurring α-amino acid and it is not the side chain of cyclohexylalanine or cyclohexylglycine.

In certain other of these embodiments, when such compounds that include a chemical labeling/linking group or chromophore or fluorphore have formulae (I) or (II), they are as defined, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, R_1 is not the side chain of cyclohexylalanine or cyclohexylglycine.

In certain other of these embodiments, when such compounds that include a chemical labeling/linking group or chromophore or fluorphore have formulae (I) or (II), they are as defined, but with the proviso that: R_1 is a side chain of a non-naturally-occurring amino acid, the side chain of R_1 is of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, unless the compounds are primary alcohols, then the non-naturally-occurring amino acid is other than norleucine or norvaline.

In certain other of these embodiments, when such compounds that include a chemical labeling/linking group or chromophore or fluorphore have formulae (I) or (II) or (III), they are as defined, but with the proviso that: R_1 is a side chain of a non-naturally-occurring amino acid, the side chain of R_1 is of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, unless the compounds are primary

alcohols, then the non-naturally-occurring amino acid is other than norleucine or norvaline.

Thus, in certain other of these embodiments in which such compounds that include a chemical labeling/linking group or chromophore or fluorphore are primary alcohols and have formulae (I) or (II), particularly formula I, they are as defined, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, it is not the side chain of norleucine or norvaline.

Thus, in certain other of these embodiments in which such compounds that include a chemical labeling/linking group or chromophore or fluorphore are primary alcohols and have formulae (I) or (II), particularly formula I, they are as defined, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, it is not the side chain of cyclohexylalanine, cyclohexylglycine, norleucine or norvaline.

In other of these embodiments, when such compounds that include a chemical labeling/linking group or chromophore or fluorphore have formulae (I) or (II) they are as defined, but with the proviso that: R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine or norvaline.

In other of these embodiments, when such compounds that include a chemical labeling/linking group or chromophore or fluorphore have formulae (I) or (II) or (III) they are as defined, but with the proviso that: R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine or norvaline.

In other of these embodiments, when such compounds that include a chemical labeling/linking group or chromophore or fluorphore have formulae (I) or (II) they are as defined, but with the proviso that: R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine, norvaline, citrulline, ornithine, 4-phenyl-2-aminobutyric acid, 1-naphthylalanine, 2-naphthylalanine, sarcosine, 2-indolinecarboxylic acid, β-alanine, β-valine, *N*-6-acetyllysine, O-4'-methyltyrosine, a substituted alanine and guanidinophenylalanine.

In other of these embodiments, when such compounds that include a chemical labeling/linking group or chromophore or fluorphore have formulae (I), (II) or (III) they are as defined, but with the proviso that: R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine, norvaline, citrulline, ornithine, 4-phenyl-2-aminobutyric acid, 1-naphthylalanine, 2-naphthylalanine, sarcosine, 2-indolinecarboxylic acid, β-alanine, β-valine, *N*-6-acetyllysine, O-4'-methyltyrosine, a substituted alanine and guanidinophenylalanine.

In certain other of these embodiments, when such compounds that include a chemical labeling/linking group or chromophore or fluorphore have formulae (I) or (II) they are as defined, but with the proviso that: at least one of the amino acid residues in the resulting di-peptide or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5, preferably R_1, is a side chain of a non-naturally-occurring amino acid, R_1 is not cyclohexylalanine, and the at least one non-naturally-occurring amino acid (or side chain thereof) is other than norleucine or norvaline, unless the resulting residue is a halo-substituted alcohol, particularly fluoro-substituted alcohols.

In other of these embodiments, when such compounds that include a chemical labeling/linking group or chromophore or fluorphore have

formulae (I) or (II) they are as defined and at least one of R_1, R_3 and R_5, preferably R_1 or R_5, includes at least one unsaturated bond. Thus at least one of R_1, R_3 and R_5 is a straight or branched carbon chain containing at least one unsaturated bond, preferably a double bond, and 2 to 10, preferably 3 to 7, more preferably 4 to 6, carbon atoms in the chain. Such side chains include, but are not limited to, substituted and unsubstituted propenes, butenes, pentenes, such as, 2-methyl-propenyl and 2-butenyl, which are among the preferred residues.

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference.

As used herein, the term "alkyl" includes the straight, branched-chain and cyclic manifestations thereof, the number of carbon atoms is generally specified. Where not specified the alkyl groups preferably contain from about 1 up to about 10 or 12, more preferably 1 to 6 or 7, and most preferably 4 to 6 carbons. Exemplary of such moieties are methyl, ethyl, propyl, cyclopropyl, isopropyl, n-butyl, t-butyl, sec-butyl, cyclobutyl, pentyl, cyclopentyl, n-hexyl, n-nonal, n-decyl, cyclohexyl, cyclohexylmethyl, cyclohexylethyl, and the like. Lower alkyl refers to alkyl groups containing six or fewer carbon atoms.

As used herein, heteroatoms are selected from O, N or S.

As used herein, heterocycle means a ring system that includes one or more heteroatoms selected from S, O or N. Heterocycles include aliphatic rings (saturated) and heteroaryl rings. Preferred cyclic groups contain one or two fused rings and include from about 3 to about 7 members in each ring.

As used herein, the term "NR_DR_E" refers to a substituent in which a nitrogen atom is bound to both the R_D and R_E substitutents.

As used herein, the term "NRR'" refers to a substituent in which a nitrogen atom is bound to both the R and R' substitutents.

The term "aryl" within the definitions of X, R_B, R_1, R_3, R_5, and R_7 includes carbocyclic and heterocyclic moieties. Preferred aralkyl and aryl moieties are phenyl, benzyl, phenethyl, 1- and 2-naphthylmethyl, 1- and 2-naphthyl, 2-, 3-, 4- pyridyl, 2- and 3-furyl, 1- and 2-indenyl, 1- and 2-thiophenyl, imidazolyl, indolyl, 2- and 3-thienyl, indole-3-ethyl and the residue of 1,2,3,4,tetrahydroisoquinoline. Other carbocycles are such fused moieties as pentalenyl, indenyl, naphthaleneyl, naphthylmethyl, azulenyl, heptalenyl, acenaphthylenyl, 9-fluorenyl, phenalenyl, phenanthrenyl, anthracenyl, triphenylenyl, pyrenyl, chryrsenyl, and naphthacenyl. Exemplary of alkynyl is propynyl. Exemplary of alkenyl moieties are 2-methyl-2-propenyl, 2-methyl-1-propenyl, propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2,2-difluoroethenyl, as well as those straight and branched chained moieties having up to two double bonds. Cyclic carbon moieties preferably contain one or two fused rings typically from 3 up to about 16, preferably 4 up to about 12 carbons.

Haloalkyl embraces such moieties as $-CF_3$, $-CF_2CF_3$, $-CF_2H$, $-CFH_2$, CH_2Cl and CH_2Br and other halo substituted lower alkyls. Exemplary of aryloxyalkenyl and aryloxyalkynyl moieties of R_A are phenoxymethyl, CF_3-substituted phenoxymethyl, benzyloxymethyl, phenoxybutyl-2-ene, 1-phenyl-1-propene, CF_3-phenoxybutyr-2-ene and CF_3-benzyloxymethyl; these moieties are preferred when R_A is other than R_1.

In those instances in which a substituent, such as the R_1, R_3, and/or R_5 moiety, embrace the residue -or side chain- of a naturally occurring α-amino acid, it is to be noted that each α-amino acid has a characteristic "R-group," the R-group being the residue -or side chain-attached to the α-carbon atom of the amino acid. For example, the residue of glycine is H, for alanine it is methyl, for valine it is isopropyl. The specific residues of the naturally occurring α-amino acids are well known

to those of skill in this art [see, e.g., A. L. Lehninger, *Biochemistry: The Molecular Basis of Cell Structure and Function*, 1970 (or any edition thereafter), Worth Publishers, NY, see, particularly Chapter 4).

As used herein, the residues of naturally occurring α-amino acids are the residues of those 20 α-amino acids found in nature which are incorporated into protein by the specific recognition of the charged tRNA molecule with its cognate mRNA codon in humans.

As used herein, certain moieties in the peptide analogs provided herein are designated according to the system of nomenclature in which the binding region of a proteinase is considered as a series of subsites, S, along the surface of the enzyme [see, Schecter and Berger (*Biochem. Biophys. Res. Comm.*, 27, 157-162 (1967)]. Each subsite binds an individual peptide residue, P. This system of nomenclature was originally designed for papain, but has been adapted to other proteases. Thus, for convenience and in keeping with the customary peptide designations, the moiety bearing the R_1 side chain (or residue) is designated as the P_1 moiety, the moiety bearing the R_3 side chain (or residue) is designated as the P_2 moiety, and that bearing the R_5 moiety is designated as the P_3 moiety.

When the R_7-$(Q)_n$- and (R_8)-$CH(R_A)$-$(Q)_n$- moieties are as defined in any of (i)-(vii) above, they are referred to as N-terminal capping, or blocking, moieties and include those moieties that protect molecules from degradation by aminopeptidases including, but not limited to, such generic groupings as arylcarbonyl, alkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, aralkylsulfonyl, alkylsulfonyl, arylsulfonyl, and other equivalently functioning groups known in the art.

As defined particularly for the capping groups herein, either individually or as a part of a larger group, "alkyl" means a linear, cyclic, or branched-chain aliphatic moiety of 1 to 20 carbon atoms; "aryl" means an aromatic moiety, e.g., phenyl, of 6 to 18 carbon atoms, unsubstituted

or substituted with one or more alkyl, substituted alkyl, nitro, alkoxy, or halo groups; "substituted alkyl" means an alkyl group having a substituent containing a heteroatom or heteroatoms such as N, O, or S; "halo" means Cl or Br; and "alkaryl" means an aryl moiety of 6 to 19 carbon atoms having an aliphatic substituent, and, optionally, other substituents such as one or more alkyl, substituted alkyl, alkoxy or amino groups.

Examples of suitable *N*-terminal blocking groups include, but are not limited to, formyl, t-butyloxycarbonyl, isopropyloxycarbonyl, allyloxycarbonyl, acetyl, trifluoracetyl, methyl, ethyl, benzyl, benzoyl, acetoacetyl, chloroacetyl, succinyl, phthaloxy, phenoxycarbonyl, methoxysuccinyl, p-methoxybenzenesulfonyl, p-toluenesulfonyl, isovaleroyl, methanesulfonyl, benzyloxycarbonyl, substituted benzyloxycarbonyl, adipyl, suberyl, thalamido-, morpholino-, azelayl, dansyl, tosyl, 2,4-dinitrophenyl, fluorenylmethoxycarbonyl, methoxyazelayl, methoxyadipyl, methoxysuberyl, 1-adamantanesulfonyl, 1-adamantaneacetyl, 2-carbobenzoyl, phenylacetyl, t-butylacetyl, bis[(1-methyl)methyl]acetyl, and thioproline.

As used herein, moieties useful in methods of identifying and/or isolating proteases include, but are not limited to, chemical labeling/linking groups, chromophores and fluorophores.

As used herein, a chromophore is a chemical group that absorbs light at a specific frequency when in a free state (i.e., uncoupled from the peptide compounds described herein) and thereby imparts a detectable color (e.g., detectable spectrophotometrically). Chromophores suitable for use in generating chromogenic substrates are well known to those of skill in the art. Preferred chromophores include p-nitranilide, 4-methoxy-β-naphthylamide and para- or ortho-nitrophenols.

As used herein, a fluorphore is a chemical group that, when in a free state (i.e., uncoupled from the peptide compounds described herein),

absorbs radiation of one wavelength and emits radiation of a different wavelength which is detectable using standard fluorometric techniques. The process of fluorescence refers to emission of a photon by a molecule in an excited singlet state. Fluorphores suitable for use in generating fluorogenic substrates are well known to those of skill in the art [see, for example, Nicholson et al. Nature 376:37-43 (1995)] and include 7-amino-4-methylcoumarin and 5(6)-carboxy-fluorescein with 7-amino-4-methylcoumarin being preferred.

As used herein, a chromogenic or fluorogenic substrate is a molecule containing a chromophore or fluorphore that does not emit color or fluorescence. Alteration of the substrate in such a way as to effect removal of the chromophore or fluorphore from the remainder of the substrate molecule results in emission of color or fluorescence from the released free chromophore or fluorphore. Chromogenic and fluorogenic substrates are represented by any of the compounds of formulae I, II and III in which X is a chromophore or fluorphore.

As used herein, chemical labeling/linking groups are chemical moieties characterized by being readily detectable through a variety of means, e.g., spectrophotometry, fluorometry, radiography, scintillation counting. The labeling group includes a label portion which is bonded to a chemical linker which, in turn, is bonded to the molecule being labeled. The labeling group can be detectable in and of itself or through formation of a complex with a detectable moiety. Chemical labeling groups are well known to those of skill in the art and include derivatives of biotin (which may be detected by binding to streptavidin conjugated to horseradish peroxidase). Chemical linking groups are chemical moieties that permit efficient coupling of the molecule to which they are linked to solid supports. The chemical linking groups include chemical linkers contained in chemical labeling groups as described above and are preferably primary amines such as 6-amino caproic acid and amino decanoic acid.

As used herein, an effective amount of a compound for treating a disorder is an amount that is sufficient to ameliorate, or in some manner reduce a symptom or stop or reverse progression of a condition. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

As used herein, treatment means any manner in which the symptoms or pathology of a condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

As used herein, substantially pure means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography [TLC], gel electrophoresis and high performance liquid chromatography [HPLC], used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

As used herein, biological activity refers to the in vivo activities of a compound or physiological responses that result upon in vivo administration of a compound, composition or other mixture. Biological activity, thus, encompasses therapeutic effects and pharmaceutical

activity of such compounds, compositions and mixtures. Biological activity may be detected by in vitro assays, such as those described herein (see Example 31).

As used herein, pharmaceutical activity refers to the activity of the compounds herein to treat a disorder.

As used herein, the IC_{50} refers to an amount, concentration or dosage of a particular compound that achieves a 50% inhibition of a maximal response.

As used herein, EC_{50} refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

As used herein, a prodrug is a compound that, upon in vivo administration, is metabolized or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism in vivo, once a pharmaceutically active compound is identified, those of skill in the pharmaceutical art generally can design prodrugs of the compound [see, e.g., Nogrady (1985) Medicinal Chemistry A Biochemical Approach, Oxford University Press, New York, pages 388-392].

As used herein, amyloid precursor protein (APP) is the progenitor of deposited amyloidogenic Aβ peptides (Aβ) found in the senile plaques in patients with diseases, such as Alzheimer's disease (AD), that are characterized by such deposition. α-sAPP is an alternative cleavage

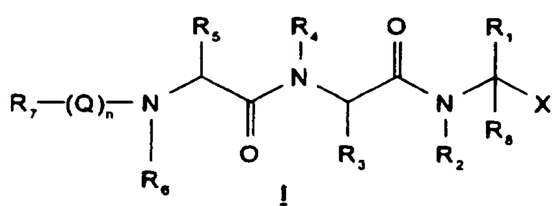
product of APP; its formation precludes formation of Aβ. Total sAPP (often designated as sAPP) refers to any soluble N-terminal fragment of APP, including α-sAPP, that is released upon cleavage of APP.

As used herein, Cha is cyclohexylalanine, and Chg is cyclohexylglycine.

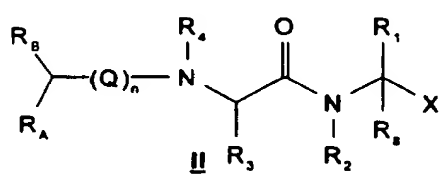
As used herein, the abbreviations for any substituent groups, protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature [see, (1972) Biochem. 11:1726]. Some exemplary abbreviations include: BOC is benzyloxycarbonyl; BOP is benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate; DCC is dicyclohexylcarbodiimide; DDZ is dimethoxydimethylbenzyloxy; DMT is dimethoxytrityly; FMOC is fluorenylmethyloxycarbonyl; and TFA is trifluoroacetic acid.

A. The tri- and dipeptide analogs and amino acid analogs

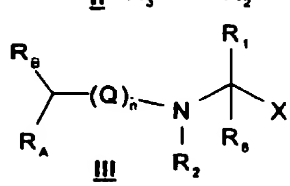
Compounds of formulae (I), (II) and (III):



I



II



III

or the hydrates and isosteres, diastereomeric isomers and mixtures thereof, or pharmaceutically acceptable salts thereof, in which X is selected as described above; and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi) or (vii) as described above are provided, but with the proviso that, when the compounds have formula (I) or (II): (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid and X is a tertiary or secondary haloalkyl alcohol, R_1 is not the side chain of cyclohexylalanine or cyclohexylglycine.

In other embodiments, when the compounds have formula (III), as defined above, when X is a tertiary or secondary haloalkyl alcohol, then R_1 is the side chain of a non-naturally-occurring α-amino acid and it is not the side chain of cyclohexylalanine or cyclohexylglycine.

In certain other embodiments, the compounds have formulae (I) or (II), as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, R_1 is not the side chain of cyclohexylalanine or cyclohexylglycine.

In certain other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): R_1 is a side chain of a non-naturally-occurring amino acid, the side chain of R_1 is of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, unless the compounds

are primary alcohols, then the non-naturally-occurring amino acid is other than norleucine or norvaline.

In certain other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I), (II) or (II): R_1 is a side chain of a non-naturally-occurring amino acid, the side chain of R_1 is of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, unless the compounds are primary alcohols, then the non-naturally-occurring amino acid is other than norleucine or norvaline.

Thus, in certain other embodiments in which the compounds are primary alcohols, the compounds have formulae (I) or (II), particularly formula I, as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, it is not the side chain of norleucine or norvaline.

Thus, in certain other embodiments in which the compounds are primary alcohols, the compounds have formulae (I) or (II), particularly formula I, as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, it is not the side chain of cyclohexylalanine, cyclohexylglycine, norleucine or norvaline.

In other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine or norvaline.

In other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I), (II) or (III): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine or norvaline.

In other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine, norvaline, citrulline, ornithine, 4-phenyl-2-aminobutyric acid, 1-naphthylalanine, 2-naphthylalanine, sarcosine, 2-indolinecarboxylic acid, *β*-alanine, *β*-valine, *N*-6-acetyllysine, O-4′-methyltyrosine, a substituted alanine and guanidinophenylalanine.

In other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I), (II) or (III): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine, norvaline, citrulline, ornithine, 4-phenyl-2-aminobutyric acid, 1-naphthylalanine, 2-naphthylalanine, sarcosine, 2-indolinecarboxylic acid, *β*-alanine, *β*-valine, *N*-6-acetyllysine, O-4′-methyltyrosine, a substituted alanine and guanidinophenylalanine.

In certain other embodiments, the compounds have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): at least one of the amino acid residues in the resulting di-peptide or tri-peptide is a non-naturally-occurring *α*-amino acid or at least one of the R_1, R_3 and R_6, preferably R_1, is a side chain of a non-naturally-occurring amino acid, R_1 is not cyclohexylalanine, and the at least one non-naturally occurring amino acid (or side chain thereof) is other than norleucine or norvaline, unless the resulting residue is a halo-substituted alcohol, particularly fluoro-substituted alcohols. Such

compounds include, but are not limited to: (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide and *N*-valeroyl-L-Leu *N*-[3-(1 ,1,1-trifluoro-2-heptanol)]amide.

In other embodiments, the compounds have formulae (I) or (II) and at least one of R_1, R_3 and R_5, preferably R_1 or R_5, includes at least one unsaturated bond. Thus at least one of R_1, R_3 and R_5 is a straight or branched carbon chain containing at least one unsaturated bond, preferably a double bond, and 2 to 10, preferably 3 to 7, more preferably 4 to 6, carbon atoms in the chain. Such side chains include, but are not limited to substituted and unsubstituted propenes, butenes, pentenes, such as, 2-methyl-propenyl and 2-butenyl, which are among the preferred residues.

Preferred among these compounds, subject to or defined with any of the provisos, are those in which:

R_1 is preferably H or a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated, preferably a double bond, or is cyclic moiety containing from 5 to 6 members, and is more preferably methyl, 2-methyl propene, 2-butene, cyclohexyl, lower alkyl-substituted cyclohexyl or cyclohexylmethyl, hydroxyphenyl, isopropyl, toluyl, t-butyl, isobutyl, n-butyl, 1-aminobutyl, methylethylthioether and is more preferably n-butyl, toluyl, isobutyl or cyclohexylmethyl;

R_2, R_4 and R_8 are each independently selected from among H or C_{1-4} alkyl, and more preferably methyl or ethyl;

R_3 is H, C_{1-4} alkyl, aryl, particularly phenyl, naphthyl and hydroxyphenyl, 1-aminobutyl, acetamide, and more preferably *iso*-butyl, benzyl, phenyl or toluyl;

R_5 is C_{1-4} alkyl, and more preferably *iso*-butyl;

R_6 is H or C_{1-4} alkyl, and more preferably H or methyl;

R_7 - $(Q)_n$ is acyl (Ac), benzyloxycarbonyl (Cbz), 9-fluorenylmethylcarbonate (Fmoc), BOC, tosyl, with Cbz, Ac and Fmoc being more preferred, and Cbz and Ac most preferred;

Q is -C(O)-, -S(O)$_2$- and -O-C(O)-, with -C(O)- and -O-C(O)- being more preferred, and -O-C(O)- most preferred;

R_B is C_{1-4} alkyl or C_{2-4} alkenyl, and more preferably *iso*-butyl;

R_A is $-(T)_m-(D)_m-R_1$; in which T is oxygen or nitrogen, with oxygen being more preferred, and D is C_{1-4} alkyl or C_{2-4} alkenyl, with a mono-unsaturated C_{3-4} alkenyl being more preferred; and

X, which is as defined above, is preferably a secondary alcohol, and more preferably least one of A or B is H and the other is haloalkyl, in which the carbon chain is straight, branched or cyclic, and is preferably a lower alkyl containing 1-6 carbons, such as CF_3, C_2F_5.

Also among preferred compounds are those of formulae (I), (II) and (III) in which R_B, R_A and the atom to which each is attached and $(Q)_n$ form (2*SR*)-*N*-[(2*S*)-2-benzoxy-4-methylpentanoyl] or (2*SR*)-*N*-[(2*R*)-[2-(1'-phenyl-1'-propene)-4-methylpentanoyl or valeroyl.

Also among preferred compounds are those of formula (I) in which R_5 and R_6 and the atoms to which each is attached form a 4-6 membered heterocyclic moiety that is preferably pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl.

When R_1, R_3, and/or R_5 are a side-chain from other than a residue of a naturally occurring α-amino acid, it is preferred that such moiety is a straight or branched carbon chain, preferably containing at least one un-saturated bond, preferably a double bond, and 2 to 10, preferably 4 to 7, more preferably 4-6 carbon atoms in the chain, such as, but not limited to, 2-methyl propene and 2-butene, or is a cylic moiety, preferably containing 4-6 members, more preferably is cyclohexyl or cyclohexyl-methyl. The resulting residues including such moieties include, but are not limited to, 2-amino-4-methyl-4-pentenoic acid, 2-amino-4-hexenoic

acid, cyclohexylalanine and cyclohexylglycine; (*2S*)-2-amino-4-methyl-4-pentenoic acid and (*2S*)-2-amino-4-hexenoic acid are preferred.

When the compounds are used in the methods of treating neurodegenerative diseases and cognitive disorders provided herein, the side chains from norvaline and leucine or from norvaline and norleucine are also preferred.

In particular, preferred compounds are those in which at least one of R_1, R_3, and R_5 is 2-methyl-propene, 2-butene, cyclohexyl or cyclohexylmethyl. More preferred are those in which R_1, R_3, and R_5 are independently selected from 2-methyl-propene, 2-butene, cyclohexyl or cyclohexylmethyl, and X is $-CH(OH)C_kH_{(2k+1-s)}F_s$ in which k is 1-6, preferably 1-3, s is 0 to 2k+1; $-CH(OH)C_6H_{(5-q)}F_q$ in which q is 0 to 5, $-(CH_2)_rC(OH)CF_3$, $CH(OH)CF_3$ and $CH(OH)CHN_2$.

Preferred heterocyclic ring moieties containing R_1 and R_2 and the atoms to which they are attached, when R_8 is H, are morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl.

Preferred heterocyclic ring moieties containing R_6 and R_7 and the atoms to which they are attached when $(Q)_n$ is a carbonyl group are selected from among succinimide, phthalimide or maleimide, with phthalimide being more preferred.

Preferred heterocyclic ring moieties containing R_6 and R_7 and the atoms to which they are attached when n in $(Q)_n$ is zero are morpholino, thiomorpholino, pyrrolidinyl, V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl, or 1,2,3,4-tetrahydroisoquinoline.

Preferred moieties, when n is zero, and when R_3 and R_4 or R_5 and R_7 are taken together with the atoms to which they are attached form heterocyclic moieties are morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl.

The following are among the preferred compounds provided herein: (2*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (1*SR*)-(2*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[1-(thiazole-hexanol)]amide, (2*SR*)-*N*-Cbz-1,1,1-trifluoro-2-heptanol, (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Pro-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-HydroxyPro-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Pro-L-Leu *N*-[3-(1,1,1-trifluoro-2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-HydroxyPro-L-Leu *N*-[3-(1,1,1-trifluoro-2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*SR*)-*N*-valeroyl-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-4-phenyl-2-butanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-4-cyclohexyl-2-butanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-3-phenyl-2-propanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-3-cyclohexyl-2-propanol)]amide, (2*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-butanol)]amide, (3*SR*)-(4S)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(ethyl 2,2-difluoro-3-hydroxyoctanoate)]amide, (4*S*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-octanol)]amide, (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-methyl-3-octanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-methyl-2-heptanol)]amide, (2*SR*)-H-L-Leu *N*-[2-(ethyl 4-methyl-4-pentenoate)]amide hydrochloride, (2*SR*)-*N*-[(2*S*)-2-benzoxy-4-methylpentanoyl]-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-Leu *N*-[3-(2-hydroxy-heptanoic acid)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(methyl 2-hydroxy-heptanoate)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(benzyl 2-hydroxy-heptamide)]amide, (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(benzyl 3-hydroxy-octamide)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu N-[3-(1-furfylthio-2-heptanol)]amide, (2*SR*)-*N*-[(2*R*)-[2-(1'-phenyl-1'-propene)-4-methylpentanoyl]]-L-Leu-*N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-*N*-Ac-L-Leu-L-Leu-*N* [2-(trans-4-hexanol)]amide,

(*2SR*)-*N*-Ac-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (*2SR*)-*N*-Ac-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, *N*-dansyl-L-Leu-L-Leu-DL-norleucinol, and *N*-Ac-L-Phe-L-Leu-DL-norleucinol.

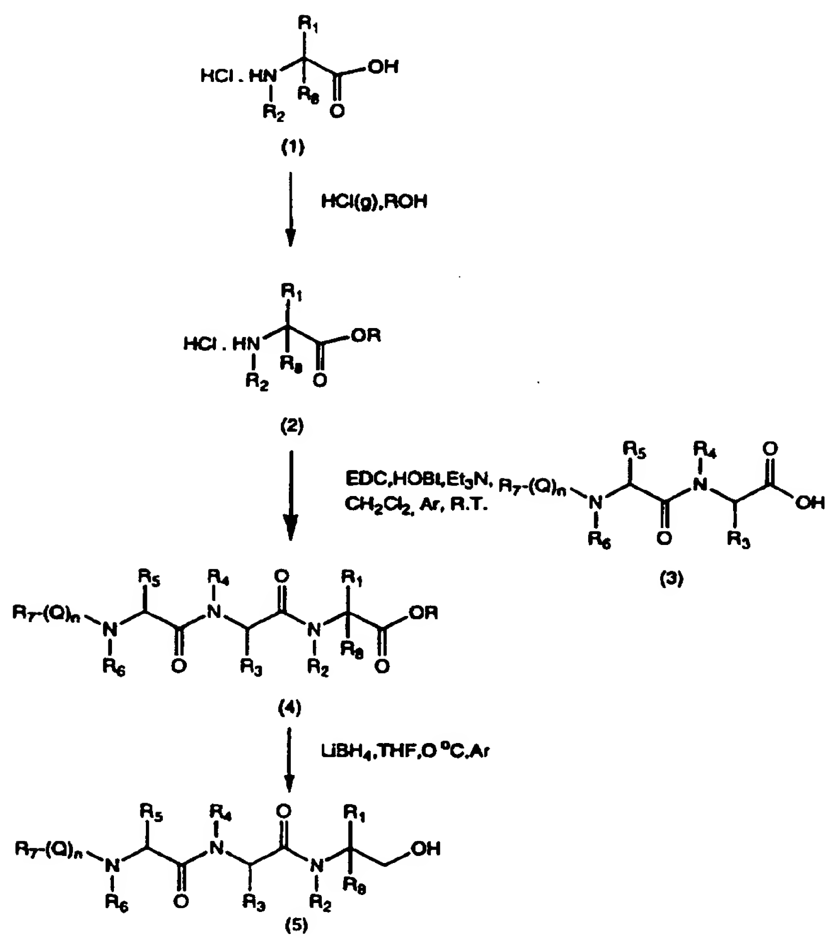
Particularly preferred compounds include: (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide and (2*SR*)-(3*SR*)-*N*-valeroyl-L-Leu *N*-[3-(1 ,1,1-trifluoro-2-heptanol)]amide.

B. Synthesis of the tri- and dipeptide analogs and amino acid analogs

1. Reaction schemes

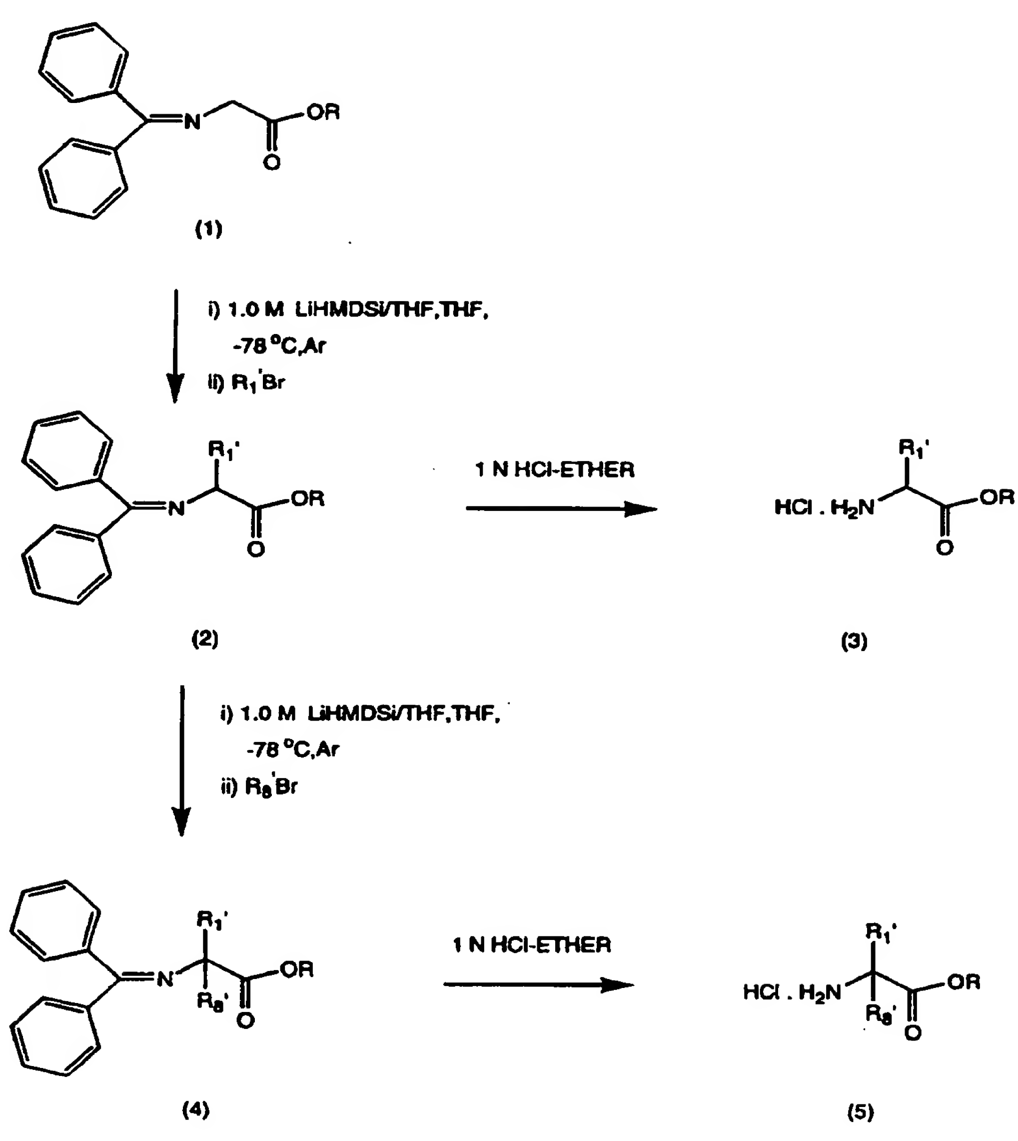
The following reaction schemes are depicted to illustrate the construction of the peptides provided herein and to illustrate the variety of reactions that may be used to prepare the intermediates from which compounds of formulae (I), (II) and (III) may be prepared.

REACTION SCHEME A



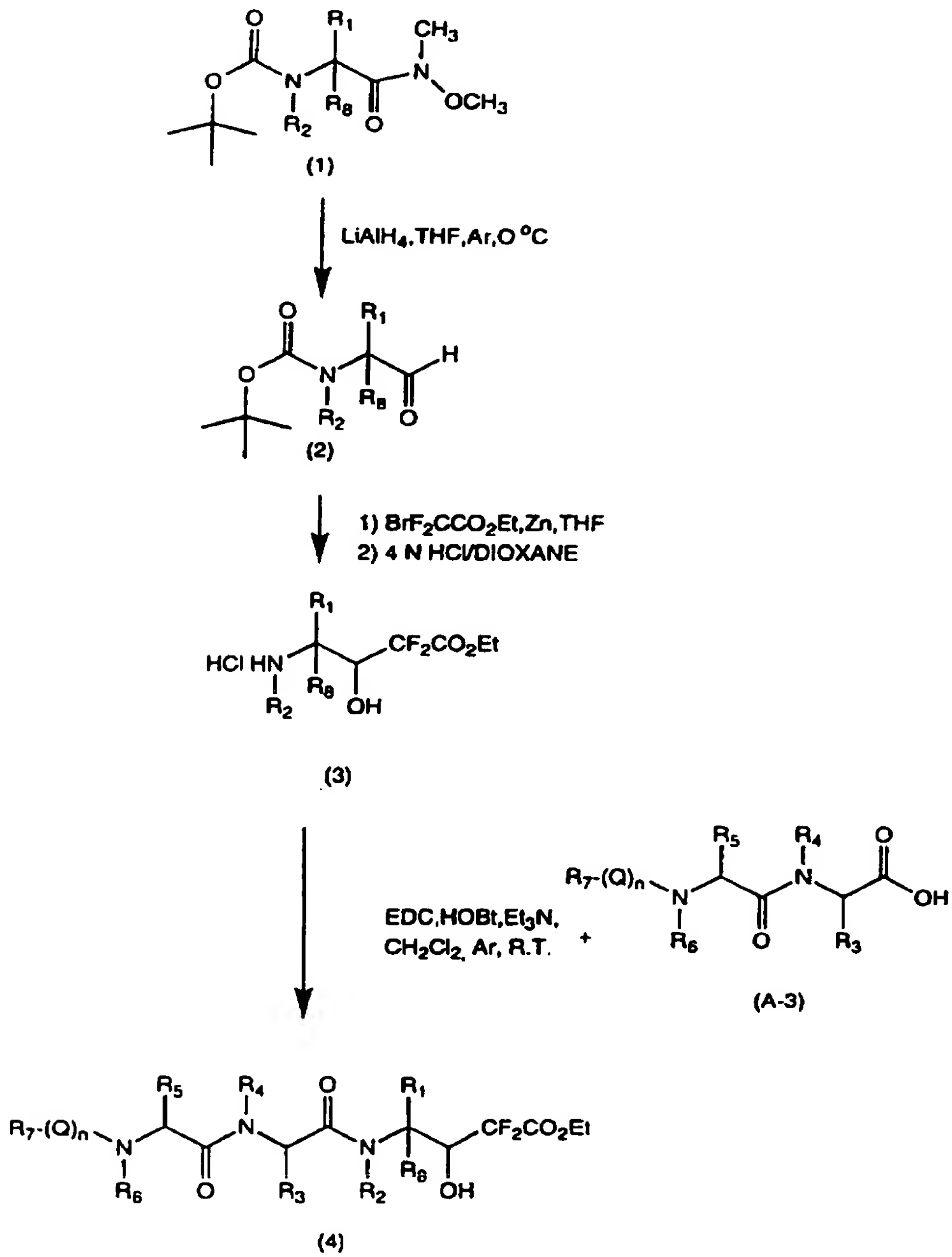
wherein the $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8$ and $(Q)_n$ are as defined above.

REACTION SCHEME B



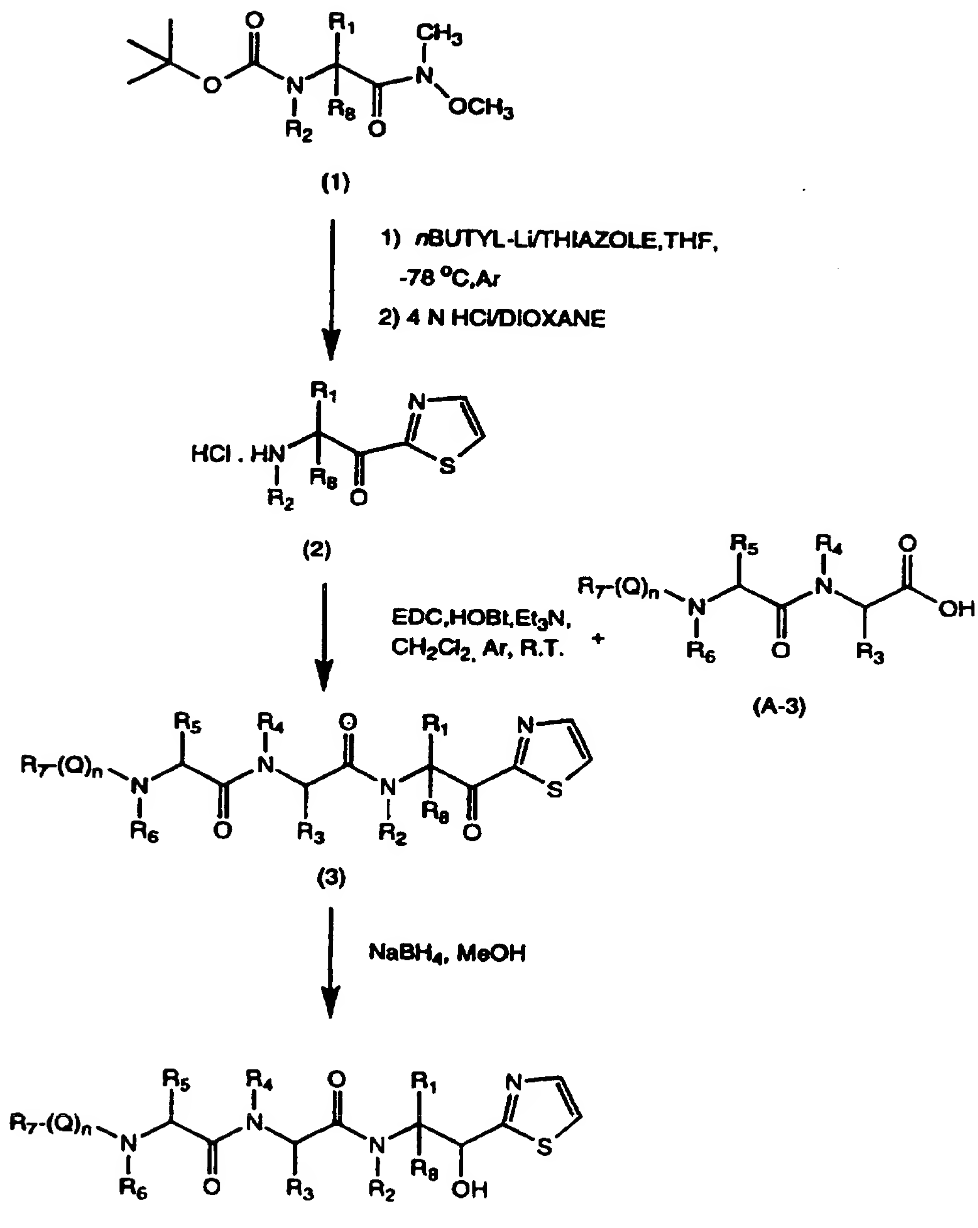
wherein R_1' is a moiety of R_1 which is not a side chain of natural α-amino acid, R_8' is C_{1-4} alkyl. R is methyl or ethyl.

REACTION SCHEME C



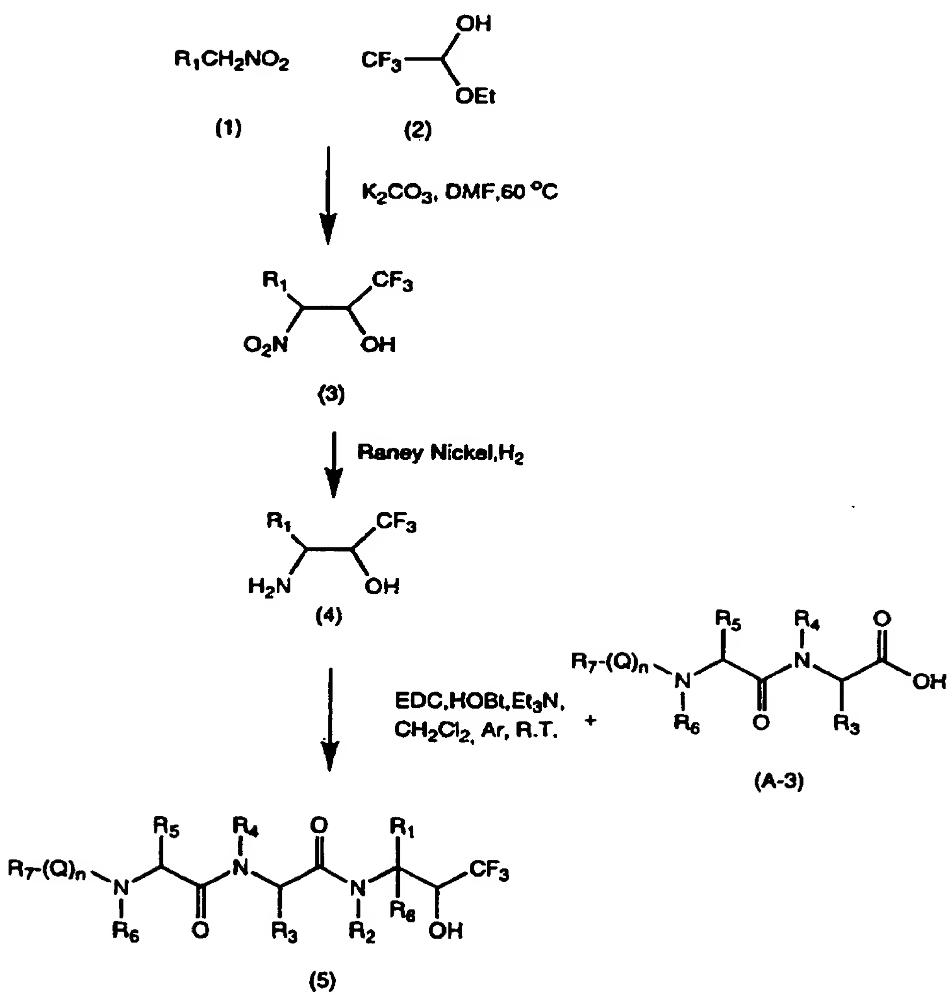
wherein the R_1,R_2,R_3,R_4,R_5,R_6,R_7,R_8 and $(Q)_n$ are as defined above.

REACTION SCHEME D



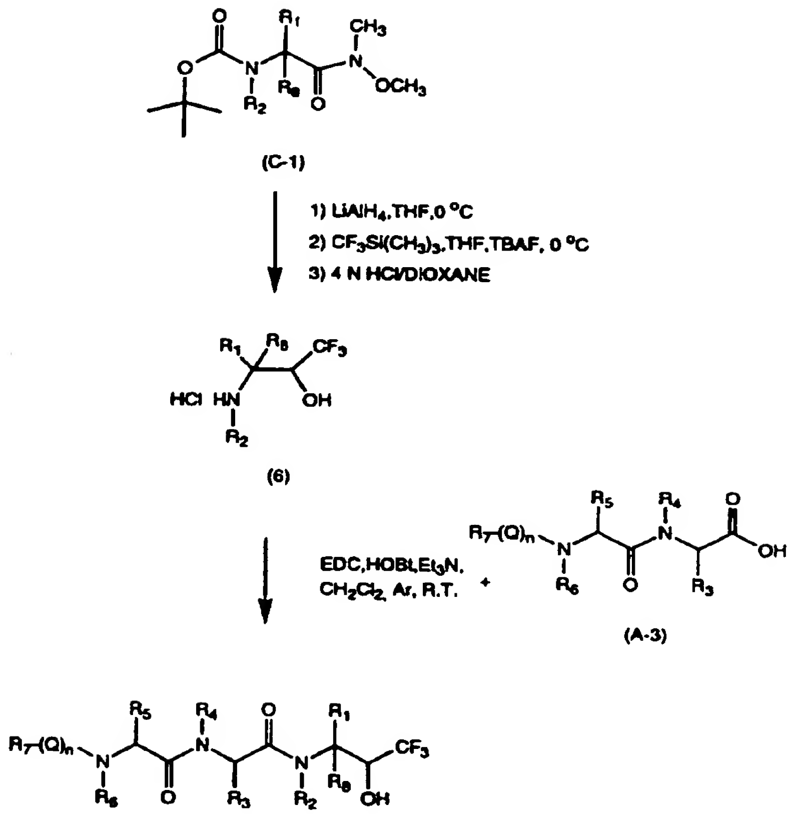
(4)

REACTION SCHEME E



wherein the R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and $(Q)_n$ are as defined above.

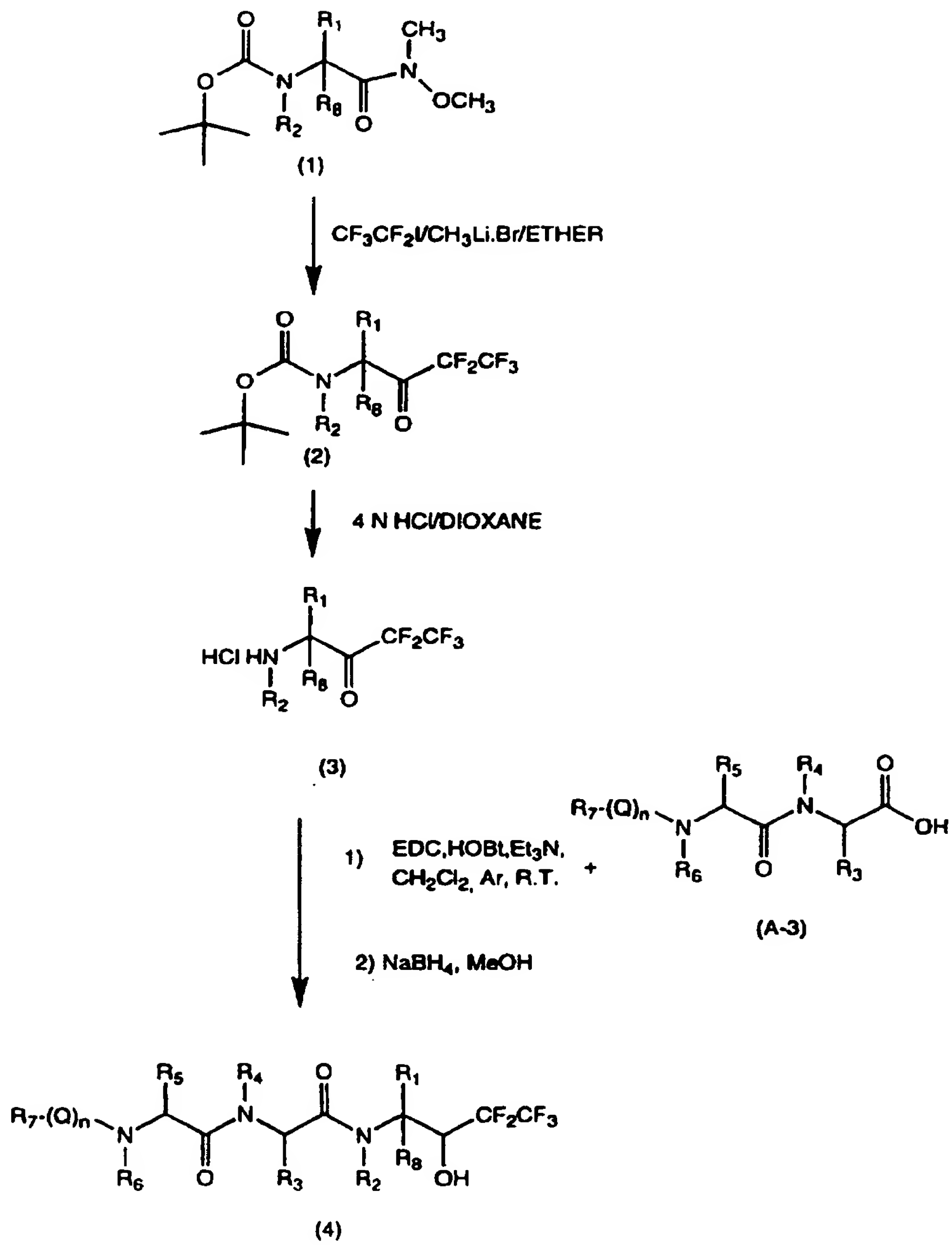
ALTERNATIVELY



(5)

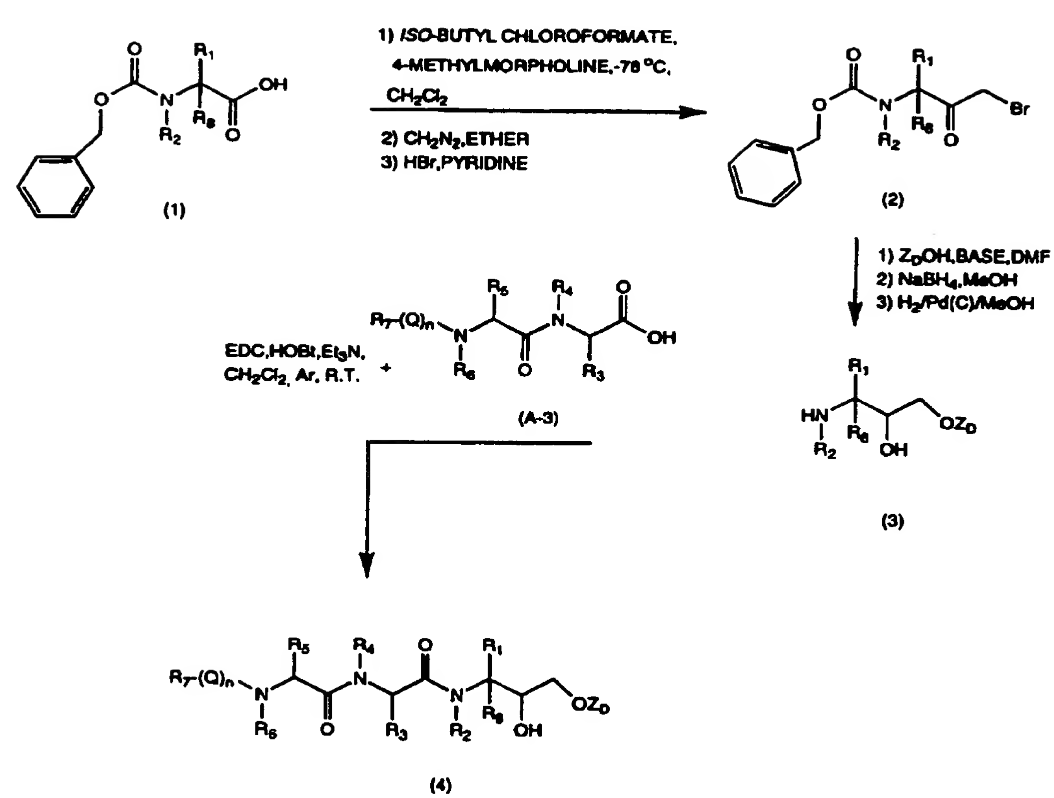
wherein the R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and $(Q)_n$ are as defined above.

REACTION SCHEME F



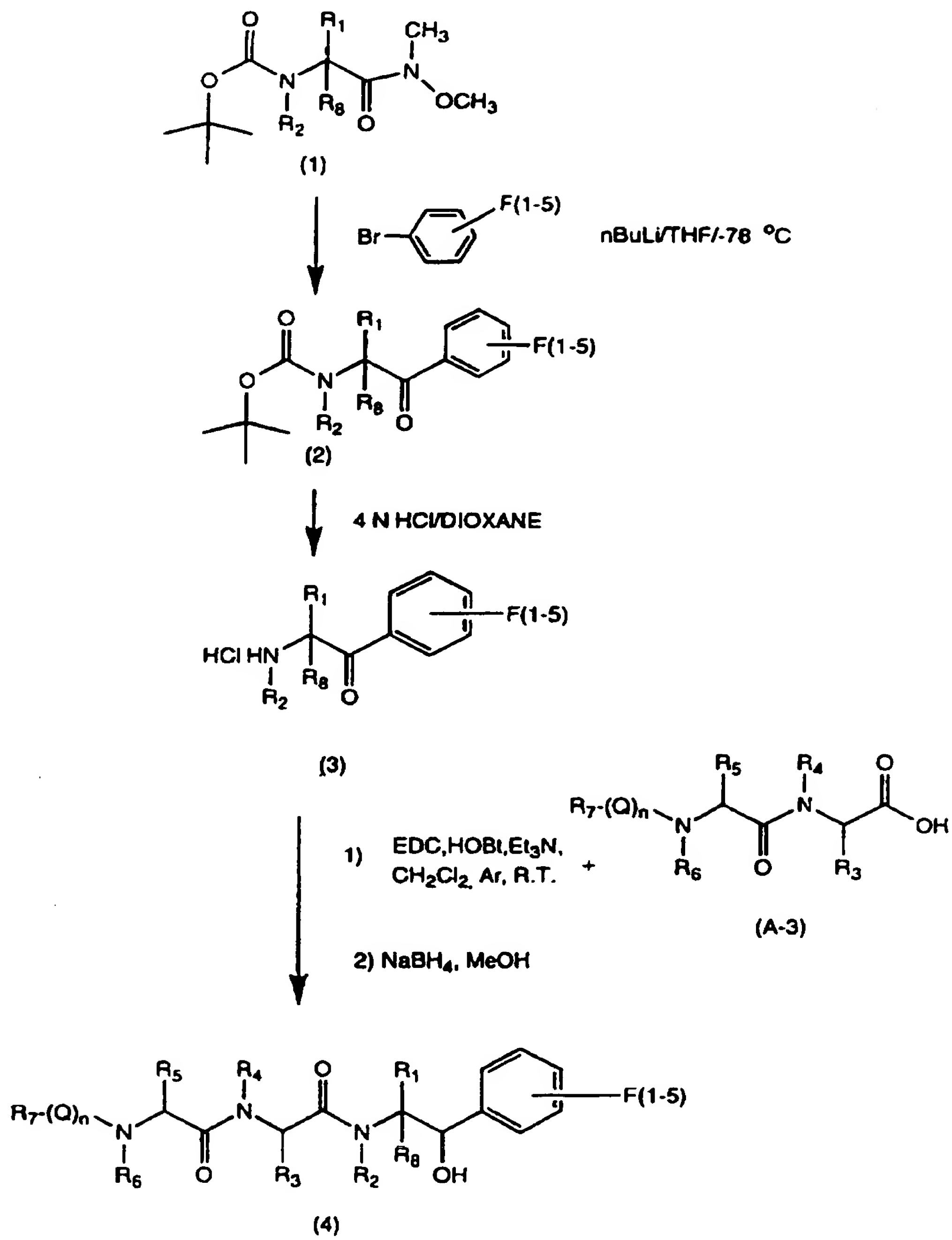
wherein the $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8$ and $(Q)_n$ are as defined above.

REACTION SCHEME G



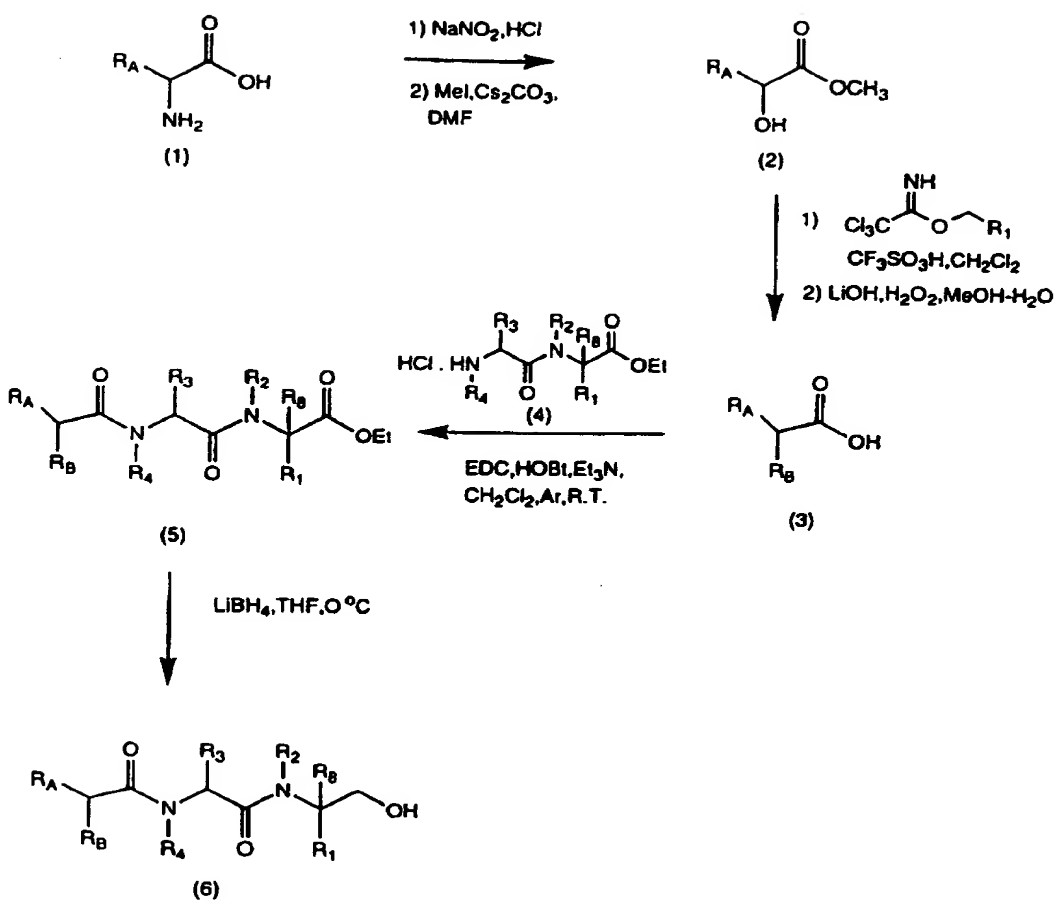
wherein the $R_1,R_2,R_3,R_4,R_5,R_6,R_7,R_8,Z_D$ and $(Q)_n$ are as defined above.

REACTION SCHEME H



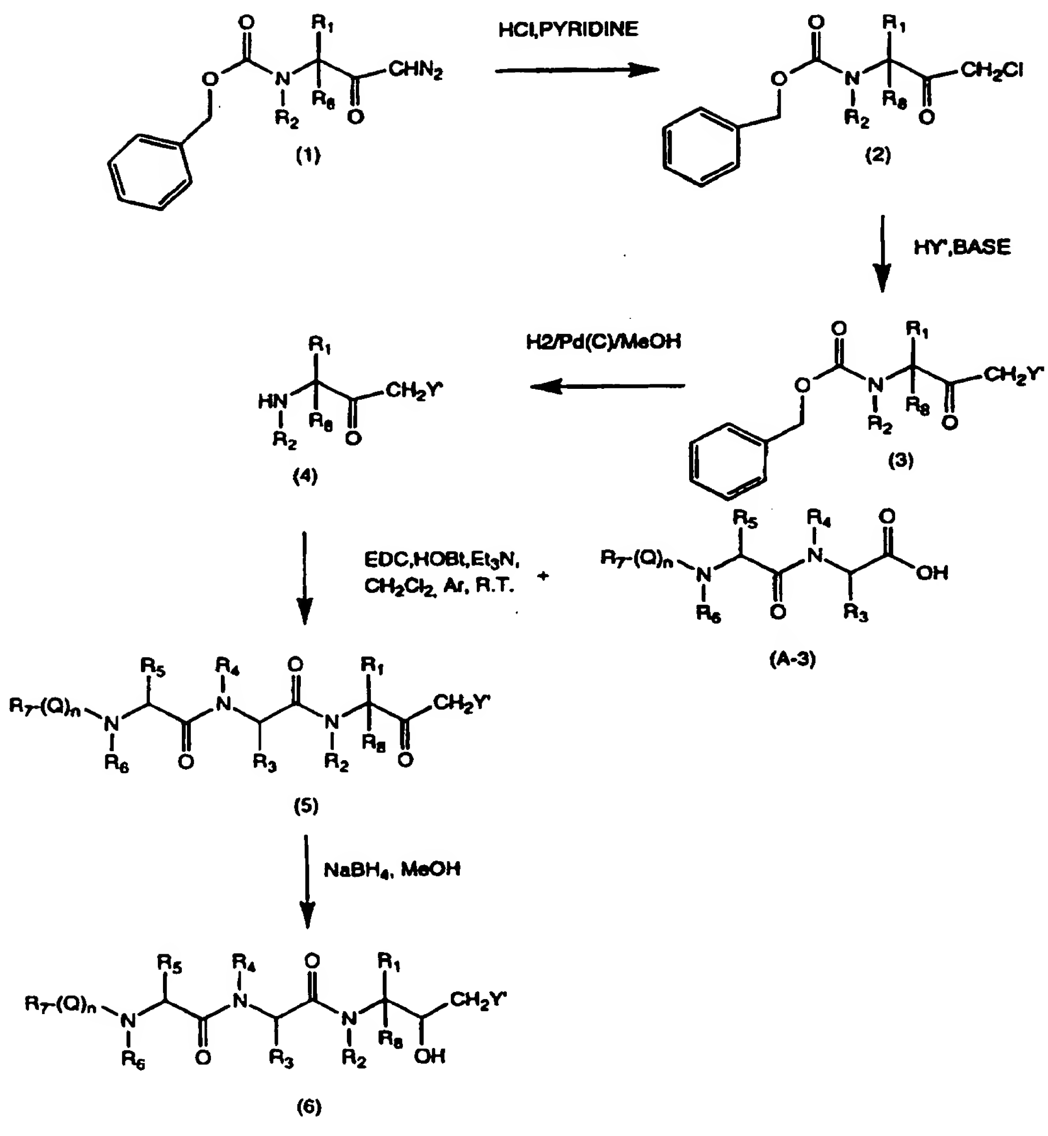
wherein the $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8$ and $(Q)_n$ are as defined above.

REACTION SCHEME I



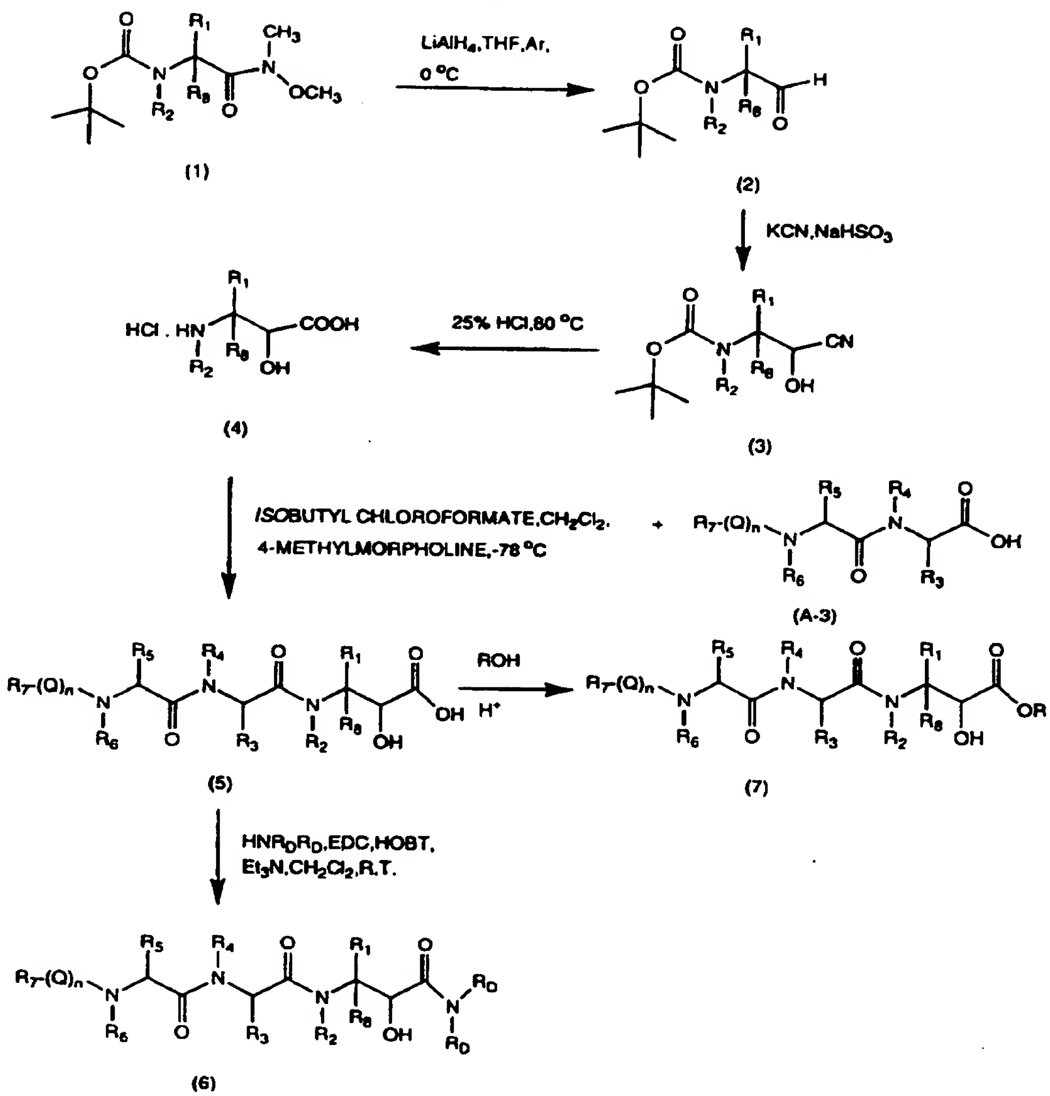
wherein the R_1,R_2,R_3,R_4,R_8,R_A and R_B are as defined above.

REACTION SCHEME J

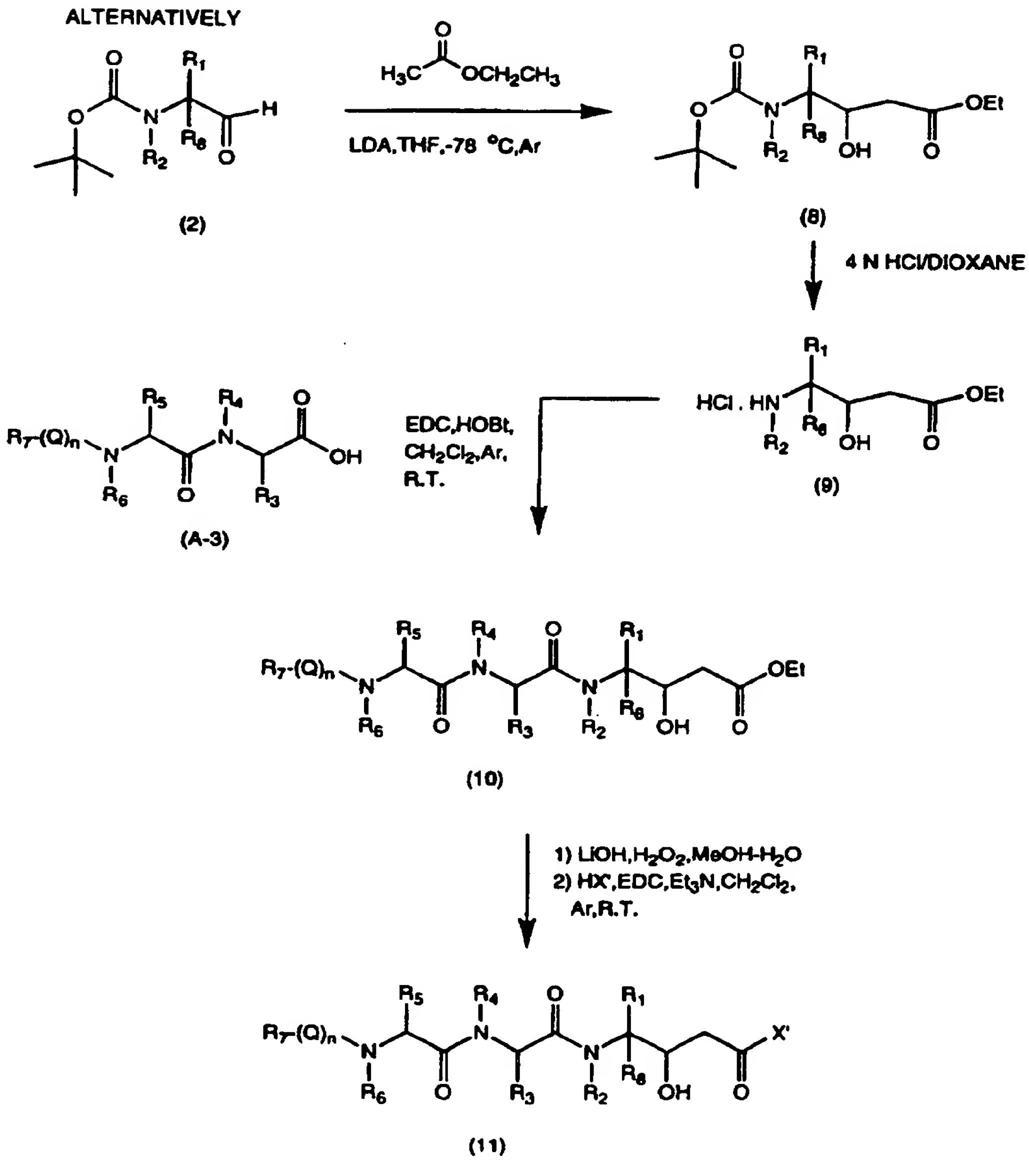


wherein Y' is OR_D,SR_D,NR_DR_D or a 5-6 ring atomed heterocycle aryl having at least one ring atom being O,S or N, and R_1,R_2,R_3,R_4,R_5,R_6,R_7,R_8 and $(Q)_n$ are as previously defined.

REACTION SCHEME K

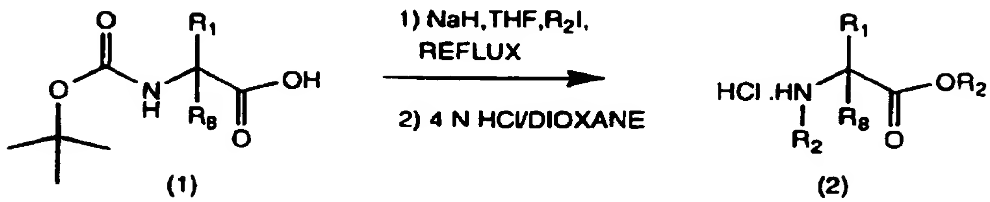


wherein the R_1,R_2,R_3,R_4,R_5,R_6, R_7, R_8 and $(Q)_n$ are as defined above.
wherein R_D is C_{1-6} alkyl,phenyl,benzyl or hydrogen.



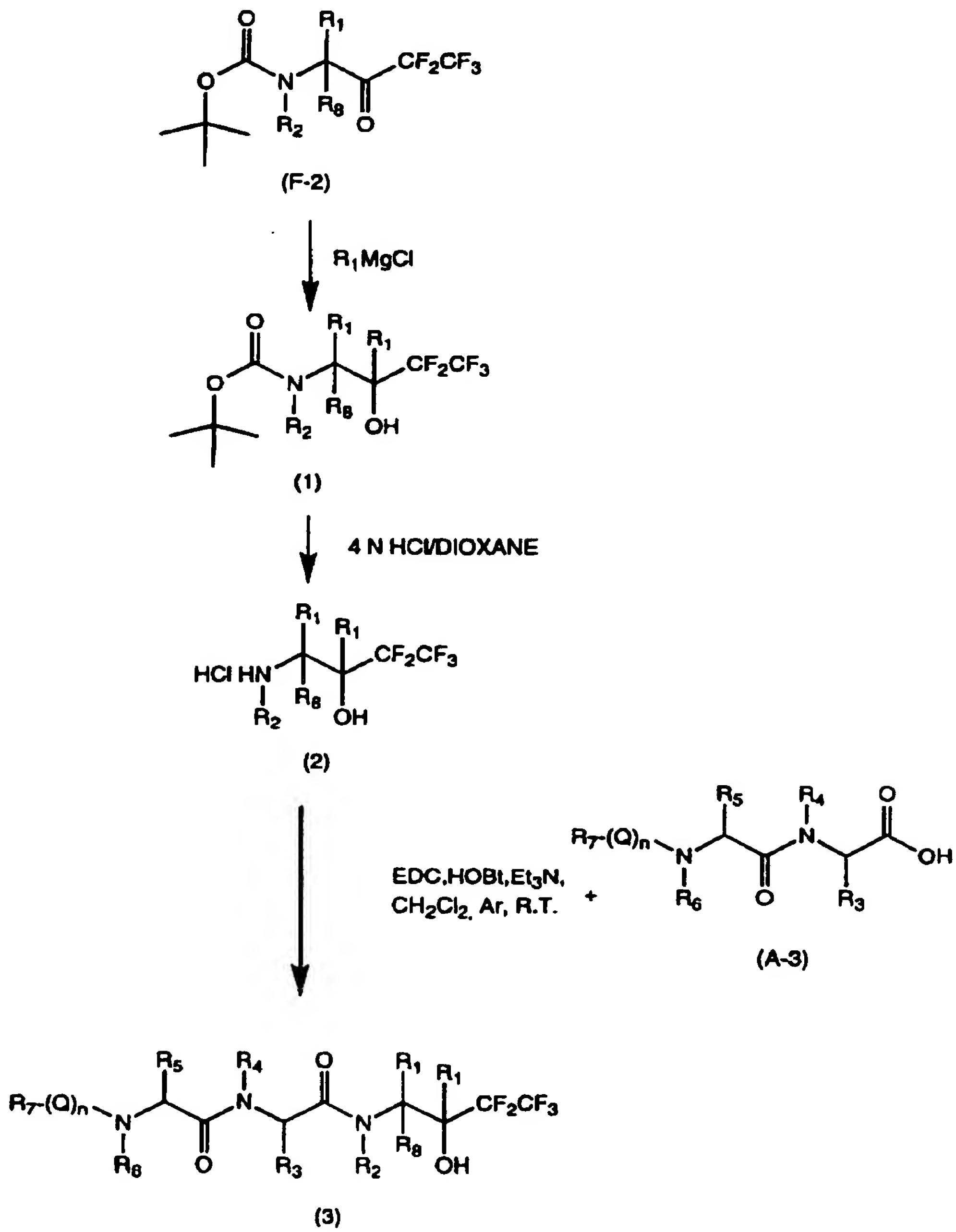
wherein the R_1,R_2,R_3,R_4,R_5,R_6, R_7,R_8 and $(Q)_n$ are as defined above.
wherein R_D is C_{1-6} alkyl,phenyl,benzyl or hydrogen and X' is OR_D or NR_DR_D.

REACTION SCHEME L



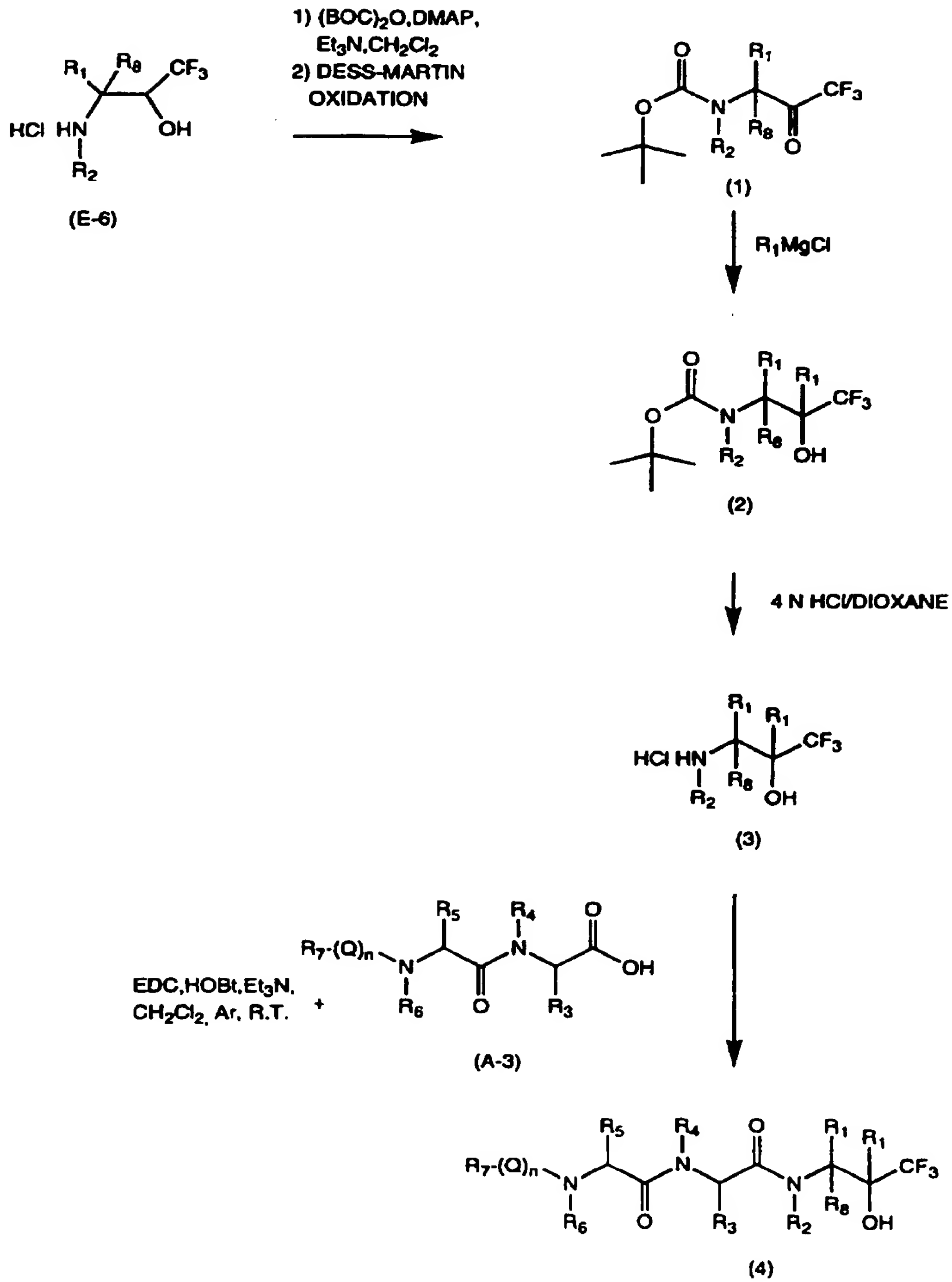
wherein the R_1,R_2 and R_8 are as defined above.

REACTION SCHEME M



wherein the R_1,R_2,R_3,R_4,R_5,R_6,R_7,R_8 and $(Q)_n$ are as defined above.

REACTION SCHEME N



wherein the R_1,R_2,R_3,R_4,R_5,R_6,R_7,R_8 and $(Q)_n$ are as defined above.

Reaction Scheme A illustrates the preparation of compounds of formulae (I), (II) and (III) in which the X moiety is a primary alcohol. In effecting the preparations, a standard Fischer esterification of the appropriate amino acid precursors produces the analogous esters (2) that are coupled with the appropriate *N*-protected P_2P_3 moieties (3) utilizing 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC; as its HCl salt) in the presence of hydroxybenzyl triazole hydrate (HOBt) and triethylamine (Et_3N). The reaction is conducted in CH_2Cl_2 at room temperature under argon or nitrogen under anhydrous conditions. The resulting compounds (4) are reduced to the desired alcohols using standard reduction conditions, including, but not limited to, the use of lithium boro-hydride ($LiBH_4$) in tetrahydrofuran (THF) at about 0° C in an inert atmosphere (Ar or N_2) under anhydrous conditions. Analogous dipeptides and *N*-protected amino acid derivatives are prepared, using substantially the same procedure, but replacing the P_2P_3 moieties [compound 3, Reaction Scheme A, hereinafter A-3] with the appropriate P_2 moiety or *N*-capping group. As noted above, the moiety bearing the R_1 side chain (or residue) is designated as the P_1 moiety, the moiety bearing the R_3 side chain (or residue) is designated as the P_2 moiety, and that bearing the R_5 moiety is designated as the P_3 moiety.

Reaction Scheme B depicts an exemplary method for the preparation of precursors of reactants, for the preparation of compounds for use in the methods herein, that are amenable to substitutions on the *α*-carbon atom. The substituents, include, but are not limited to residues of naturally- and non-naturally-occurring *α*-amino acids. In this scheme, *N*-(diphenylmethylene)glycine ethyl ester (1) is treated with lithium bis(trimethylsilyl)amide in THF under an inert atmosphere at temperatures of about -78° C, and the *in situ* generated base is reacted with the appropriate alkyl halide to effect a nucleophilic displacement. The so-alkylated intermediates (2) and (4) are subjected to hydrolysis to produce

the amines (3) and (5) that are available for appropriate use in the construction of the desired dipeptides and tripeptides in which R_1, R_3 or R_5 are side chains other than those of naturally occurring α-amino acids. Similarly, this scheme may be used to prepare compounds in which R_2, R_4 and/or R_6 are an alkylated product.

Alternatively, precursor reactants may be prepared following substantially the same procedure described by O'Donnell et al. [O'Donnell et al. (1994) Tetrahed. Lttrs. 35:9383-9386].

Reaction Scheme C illustrates the preparation of the P_1 moiety in which X is C(OH)W. In effecting this preparation, the *N*-methoxy-*N*-methylamide derivative (1) is reduced with lithium aluminum hydride under anhydrous conditions in an inert atmosphere at 0° C to produce the corresponding aldehyde (2). The difluoro-hydroxy esters [compounds (2)] are produced by a standard Reformatsky reaction [see, e.g., Rathke (1975) Org. React. 22:423-460; and March (1985) Advanced Organic Chemistry, 3d Ed., J. Wiley & Sons] followed by deprotection by hydrolysis with 4 N HCl in dioxane to obtain compounds (3). Compounds (3) are coupled to the appropriate P_2P_3 moieties (compound A-3) to obtain desired tripeptide derivatives (4). Compounds (3) may be coupled with appropriate P_2 moieties, such as $(R_A)CH(R_B)$-C(O)N(R_4)-$CH_2(R_3)$C(O)OH), to obtain the desired dipeptides, or with appropriate *N*-capping moieties to obtain desired *N*-protected amino acid derivatives.

Reaction Scheme D illustrates the preparation of compounds having a P_1 moiety in which X is C(O)W, as defined above, C_{1-6} alkyl or aralkyl. In effecting the preparations, the *N*-methoxy-*N*-methylamide derivative (1) is treated with a lithiothiazole nucleophile generated *in situ* to produce a ketothiazole, which is deprotected by hydrolysis with 4 N HCl in dioxane to obtain compounds (2). Compounds (2) are then either a) coupled to appropriate P_2P_3 moieties (A-3) to obtain desired derivatives of compound (3); or b) are coupled to appropriate P_2 moieties, such as,

but not limited to, $(R_A)CH(R_B)$-$C(O)N(R_4)$-$CH_2(R_3)C(O)OH)$, to obtain the desired dipeptides; or c) are coupled to appropriate *N*-capping moieties to obtain desired *N*-protected amino acid derivatives. Subsequent reduction of the ketone using sodium borohydride in methanol affords the desired alcohol (4). The corresponding amino acid analogs and di- and tri-peptide derivatives may be obtained by replacing the lithio derivative of thiazole with litho derivatives of other aryl, aralkyl and alkyl moieties and by following substantially the same procedures.

Reaction Scheme E illustrates the preparation of compounds of formulae (I), (II) and (III) in which the X moiety is a halomethyl alcohol. The reaction is initiated by reacting an R_1-substituted nitromethane with a trifluoromethyl acetal (2) in N,*N*-dimethylformamide (DMF) in the presence of potassium carbonate at about 60° C to yield a 1,1,1-trifluoro-2-hydroxy-3-nitro derivative (3) which are reduced with H_2 in the presence of Raney Nickel to yield the corresponding amines (4). By appropriate coupling to the appropriate dipeptide (A-3), the desired trifluoromethyl alcohols (6) of formula I may be produced. The corresponding dipeptide derivatives of the mono-, di- and tri-fluoromethyl alcohols of formulae (I)-(III) may be produced by selecting the appropriate *N*-capping group or *N*-protected amino acid derivative. Furthermore, by use of mono- and di-fluoromethyl analogs of formula (2) and by following substantially the same procedures, corresponding $-CH_2F$ and $-CHF_2$ alcohol analogs of formulae (I), (II) or (III) are produced.

Alternatively, compounds (C-1) can be reduced under standard anhydrous conditions, lithium aluminum hydride in THF at about 0° C under inert atmosphere, affords the corresponding aldehyde. The aldehyde is treated with trifluoromethyltrimethylsilane under inert atmosphere in THF at about 0° C in the presence of tetrabutylammoniumfluoride [see, Krishnamurti et al. (1991) J. Org. Chem 56:984-989], and then deprotected by hydrolysis with 4 N HCl in dioxane

to obtain compounds (6). Compounds (6) are then either a) coupled to appropriate P_2P_3 moieties (A-3) to obtain desired tripeptide derivatives (6); or b) are coupled to appropriate P_2 moieties, such as, but not limited to, $(R_A)CH(R_B)$-C(O)N(R_4)-$CH_2(R_3)$C(O)OH), to obtain the desired dipeptides; or c) are coupled to appropriate *N*-capping moieties to obtain desired *N*-protected amino acid derivatives.

Reaction Scheme F illustrates the preparation of compounds of formulae (I), (II) and (III) in which the X moiety is pentafluoromethyl alcohol. To effect preparation of these compounds, the *N*-methoxy-*N*-methylamide derivatives (1) are treated with pentafluoroethyl lithium, generated *in situ*, to produce the pentafluoroethyl ketones (2), which are deprotected by hydrolysis with 4 N HCl in dioxane to obtain compounds (3). Compounds (3) are either a) coupled to the appropriate P_2P_3 moieties (A-3) to obtain desired tripeptide derivatives; or b) coupled to appropriate P_2 moieties, such as, but not limited to, $(R_A)CH(R_B)$-C(O)N(R_4)-$CH_2(R_3)$C(O)OH) to obtain the desired dipeptides; or c) coupled with appropriate *N*-capping moieties to obtain the desired *N*-capped amino acid derivatives. The resulting pentafluoromethyl derivatives are reduced with sodium borohydride in methanol to afford the desired alcohols (4).

Reaction Scheme G illustrates the preparation of compounds of formulae (I), (II) and (III) in which the X moiety is a diazomethane that can be converted to a haloalkyloyl or haloaryloyl alcohol. In this process, the amine-protected amino acid derivatives and peptides or peptide analogs are reacted with isobutyl chloroformate in the presence of 4-methylmorpholine in CH_2Cl_2 at -78° C. The anhydride derivatives are reacted with diazomethane according to standard procedures known in the art. If desired, the diazoketones may be treated with an appropriate acid (such as, but not limited to HBr), in pyridine to afford compounds (2), which are treated with the appropriate alkyl or aryl alcohol in DMF under alkali conditions to produce the corresponding alkyloyl and aryloyl

ketones. The resulting ketones are reduced with sodium borohydride in methanol to produce the desired alcohols. The alcohols are treated with H_2/Pd(C) in methanol to afford (3). Compounds (3) are then either a) coupled to appropriate P_2P_3 moieties (A-3) to obtain desired derivatives of compound (3); or b) are coupled to appropriate P_2 moieties, such as, but not limited to, $(R_A)CH(R_B)$-C(O)N(R_4)-$CH_2(R_3)$C(O)OH), to obtain the desired dipeptides; or c) are coupled to appropriate *N*-capping moieties to obtain desired *N*-protected amino acid derivatives.

Reaction Scheme H illustrates the preparation of compounds in which the X moiety is a fluoro-substituted aryl alcohol. In effecting this scheme, the *N*-methoxy-*N*-methylamide derivatives (1) are treated with the appropriate fluoro(1-5)-substituted bromobenzene moiety in *N*-butyl lithium at -78° C under anhydrous conditions in an inert atmosphere. This generates fluorobenzene lithium *in situ*, to produce a fluoro-substituted aromatic ketones (2), which are deprotected by hydrolysis with 4 N HCl in dioxane to obtain compounds (3). By coupling compounds (3) to the appropriate P_2P_3 moieties (A-3), the corresponding fluoro-substituted aromatic ketone tripeptides (4) are produced. The ketone tripeptides are reduced with sodium borohydride in methanol to afford the desired corresponding alcohols (4). Analogous dipeptides and *N*-protected amino acid derivatives may be prepared using substantially the same procedure, but replacing the P_2P_3 moieties with the appropriate P_2 moiety or *N*-capping group.

Reaction Scheme I illustrates the formation of a dipeptide in which R_B is aryloxy, aralkoxy or an alkoxy in an enantiomeric pure isomer. The reaction is initiated by a two step process in which: (a) compounds (1) are deaminated by treatment with $NaNO_2$ in HCl; and (b) the resulting acids are esterified with an alkyl halide in the presence of DMF and cesium carbonate to produce compounds (2). These are treated with a 2,2,2-trichloroacetimate derivatives in the presence of

trifluoromethanesulfonic acid in CH_2Cl_2 to obtain the corresponding ester. The ester moieties are hydrolyzed with lithium hydroxide in peroxide and a methanol-water solvent to produce the enantiomers (3). The isomers are coupled with the appropriate P_2P_1 moieties [as esters; e.g., compounds (A-3)], and the resulting esters (5) are reduced to the desired alcohols (6).

Reaction Scheme J illustrates the preparation of compounds of formulae (I), (II) and (III) in which X is $C(O)CH_2Y$. The *N*-protected diazoketone derivatives of compound (1) are subjected to an addition reaction with an hydrohalic acid, preferably HCl, in pyridine to produce halomethyl derivatives (2), which are subjected to a nucleophilic displacement reaction using an activated anion of the desired Y moiety, (e.g., ^{-}Y), to afford compounds (3). Standard hydrogenation reactions remove the *N*-protecting group followed by the above-described coupling procedures with the desired P_2P_3 moieties (A-3) to produce compounds (5), which are reduced to the desired alcohols (6). Analogous dipeptides and *N*-protected amino acid derivatives may be prepared using substantially the same procedure but replacing the P_2P_3 moieties with the appropriate P_2 moiety or *N*-capping group.

Reaction Scheme K illustrates the preparation of compounds of formulae (I), (II) and (III) in which X is selected from moieties (a) -CH(OH)-—C(O)-NR_DR_D and (b) —CH(OH)-C(O)OR_D. The embodiment depicted in Reaction Scheme K is one in which R_D and R_E are the same, it is however not intended that R_D and R_E be limited to being the same and it is understood that the scheme setforth also encompasses embodiments in which R_D and R_E are not the same. Thus, such reactions are performed by replacing one of the R_D with R_E.

As set forth in Reaction Scheme K, the process starts by obtaining aldehyde (2) by reducing the *N*-methoxy-*N*-methylamide derivative (1), followed by preparation of the cyanohydrin (3), which is hydrolyzed to its

free acid (4) using standard and known reaction techniques. Coupling of the appropriate P_2P_3 moiety (A-3) to the acid (4) is effected by the use of an activated isobutyl chloroformate in the presence of 4-methylmorpholine at -78° C in an inert atmosphere under anhydrous conditions to afford the acid (5). The acid (5) may be esterified to its corresponding ester or may be coupled with an amine (NR_DR_D) to produce the desired amide (6). Analogous dipeptides and *N*-protected amino acid derivatives may be prepared using substantially the same procedure, but replacing the P_2P_3 moieties with the appropriate P_2 moieties or *N*-capping groups.

Alternatively, compounds (2) may be transformed to their *N*-protected (preferably protected by a BOC group) alkyl ester by reaction with ethylacetate in the presence of LDA to produce compounds (8) which are hydrolyzed with 4 N HCl in dioxane to remove the protecting group to produce the corresponding *β*-hydroxy ethyl esters (9). These esters are then coupled with compounds (A-3) and the resulting compounds are hydrolyzed to their *β*-hydroxy acids or they may be coupled to form their *β*-hydroxyamides of compounds (11).

Reaction Scheme L illustrates the process by which compounds of formulae (I), (II) and (III) in which R_2, R_4, or R_6 are an R_D moiety other than H. This procedure uses standard *N*-protection, *N*-alkylation - esterification and de-protection procedures such as those exemplified in the depicted schemes. Although the reaction scheme depicts *N*-alkylation at the projected P_1 moiety, any of the P_2 and P_3 moieties may be similarly *N*-alkylated by appropriate selection of the starting materials followed by the coupling procedures required to construct the desired peptides and amino acid derivatives of formulae (I), (II) and (III).

Reaction Scheme M illustrates the process by which compounds of formulae (I), (II) and (III) in which X is a tertiary alcohol, particularly haloalkyl-substituted tertiary alcohols are prepared. Compounds (F-2)

[see, Scheme F] are converted to tertiary alcohols, such as a pentafluoroethyl-substituted tertiary alcohol, by treatment with an analogous Grignard or lithium derivative by standard procedures known in the art. These compounds are deprotected with 4 N HCl in dioxane to produce compounds (2). Compounds (2) are either a) coupled to the appropriate P_2P_3 moieties (A-3) to obtain desired tripeptide derivatives; or b) coupled to appropriate P_2 moieties, such as, but not limited to, $(R_A)CH(R_B)$-C(O)N(R_4)-$CH_2(R_3)$C(O)OH) to obtain the desired dipeptides; or c) coupled with appropriate *N*-capping moieties to obtain the desired *N*-capped amino acid derivatives. Using analogous methods, but starting with the trifluoromethyl derivative of (F-2) or other such derivative, the trifluoromethyl or corresponding derivative may be prepared.

Reaction Scheme N illustrates another process by which compounds of formulae (I), (II) and (III) in which X is a tertiary alcohol are prepared. The precursors (E-6) are treated with $(BOC)_2$ under standard amine-protecting conditions, followed by oxidation with the Dess-Martin reagent of the trifluoromethyl alcohol to give *N*-BOC trifluoromethyl ketones (1). Reaction of (1) with the appropriate Grignard or lithium derivative affords the tertiary alcohol (2). Deprotection by hydrolysis with 4 N HCl in dioxane produces (3). Compounds (3) are either a) coupled to the appropriate P_2P_3 moieties (A-3) to obtain desired tripeptide derivatives (4); or b) coupled to appropriate P_2 moieties, such as, but not limited to, $(R_A)CH(R_B)$-C(O)N(R_4)-$CH_2(R_3)$C(O)OH) to obtain the desired dipeptides; or c) coupled with appropriate *N*-capping moieties to obtain the desired *N*-capped amino acid derivatives.

Throughout the above presentation of the methods useful for preparing the compounds herein, particularly as it relates to the foregoing reaction schemes, the full embodiment of the entire scope of the compounds (as defined in formulae (I), (II) and (III)) was not depicted within all of the structures illustrated for each of the reactants and end-

products. The state of the art is such that one of skill in the art would be able to extend these specific illustrations to embrace the implied generic teachings by the use of analogy reasoning to prepare the desired compounds embraced within the scope of formulae (I), (II) and (III). For example, one of skill in the art could utilize the final product of Reaction Scheme A in preparing any of the compounds of formulae (I), (II) and (III) bearing the R_1 side chain functionality, which is other than a residue of a naturally occurring α-amino acid. Similarly, in Reaction Scheme D, the preparation of a thiazole derivative is achieved by coupling the *N*-methoxy-*N*-methylamide derivative of a precursor for preparing a depicted tripeptide (3). A dipeptide bearing a thiazole derivative could be prepared by the application of the analogy reasoning possessed by a person of skill in the art. Similarly, lithio derivative of another heterocycle in which X is C(O)aryl and the aryl moiety is other than a thiazole embraced within the scope of the compounds herein could be prepared.

Thus, the scope of those compounds that can be prepared by the methods of the foregoing reaction schemes is not limited to the specific compounds depicted but rather to those compounds defined by formulae (I), (II) and (III) using the teachings provided herein and known to those of skill in the art, including the above-discussion and Examples below.

2. Procedures to effect the reaction schemes

The construction of the tri- and dipeptide analogs and amino acid analogs of Formulae (I), (II) and (III) may be effected using procedures and techniques known in the art and described herein. Many of the necessary starting materials and the reactants utilized are known and may also be commercially available. In those instances in which they are not generally available, they may readily be generated by analogous use of known chemical processes and techniques readily available in the scientific and patent literature or as described herein.

As the reaction schemes depicted herein (Schemes A-N) extensively utilize coupling and oxidation procedures, the following elaborates a variety of the procedures that may be functional alternatives to those specifically mentioned within the depicted schemes. As a preferred oxidation procedure, the Swern oxidation is effected by reacting 2 to 10 equivalents of dimethyl sulfoxide (DMSO) with about 1 to 6 equivalents of trifluoroacetic anhydride [$(CF_3CO)_2$)] or oxalyl chloride [-$(COCl)_2$]. The reactants are dissolved in an inert solvent, e.g., methylene chloride (CH_2Cl_2), the reactor is under an inert atmosphere under anhydrous conditions at temperatures of about -80° C to -50° C to form an *in situ* sulfonium adduct to which is added about 1 equivalent of the alcohols (e.g., A-4). Preferably, the alcohols are dissolved in an inert solvent, e.g., CH_2Cl_2 or minimum amounts of DMSO, and the reaction mixture is allowed to warm to about -50° C (for about 10-20 minutes) and then the reaction is completed by adding 3 to 10 equivalents of a tertiary amine, e.g., triethylamine, *N*-methyl morpholine, etc. Following oxidation, the desired intermediates are isolated and are ready for the next step in the reaction sequence.

A modified Jones oxidation procedure may conveniently be effected by reacting the alcohols with pyridinium dichromate by contacting the reactants in a water-trapping sieve powder, (e.g., a grounded 3 Angström molecular sieve) in the presence of glacial acetic acid at about 5° C to 50° C, preferably at room temperature.

Alternatively, 1 to 5 equivalents of a chromic anhydride-pyridine complex [i.e., a Sarett reagent prepared *in situ* (see, e.g., Fieser and Fieser "Reagents for Organic Synthesis" Vol. 1, pp. 145 and Sarett et al. (1953) J. Am. Chem. Soc. 25:422] that is prepared *in situ* in an inert solvent (e.g., CH_2Cl_2) in an inert atmosphere under anhydrous conditions at about 0° C to 50° C to which complex is added 1 equivalent of the

alcohols allowing the reactants to interact for about 1 to 15 hours, followed by the isolation of the desired product.

Another alternative process for the converting of alcohols to the desired ketones is an oxidation reaction that employs periodane [i.e., 1,1,1-triacetoxy-1,1-dihydro, 1,2-benzoxidol 3-(1-H)-one (see Dess Martin (1983) J. Org. Chem. 48:4155]. This oxidation is effected by contacting 1 equivalent of the alcohols with 1 to 5 equivalents of periodane (preferably 1.5 equivalents) in suspension in an inert solvent (such as, but not limited to CH_2Cl_2) under an inert atmosphere (preferably nitrogen) under anhydrous conditions at about 0° C to 50° C (preferably room temperature), and allowing the reactants to interact for about 1 to 48 hours.

A solid phase sequential coupling procedure can be performed using established methods such as use of an automated peptide synthesizer. In this procedure, an amino protected amino acid is bound to a resin support at its carboxyl terminus, the protected amine is deprotected where the peptide linkage is desired, the amino group neutralized with a base and the next amino protected amino acid in the desired sequence is coupled in a peptide linkage. The deprotection, neutralization and coupling steps are repeated until the desired peptide is synthesized. The compounds provided herein are thus synthesized from their carboxyl terminal end to their amino terminal end. The amino protected amino acid can be a conventional amino acid, a derivative or isomer thereof, or a spacer group. The resin support employed can be any suitable resin conventionally employed in the art for the solid phase preparation of polypeptides. The preferred resin is polystyrene which has been cross-linked with from about 0.5 to about 3% divinyl benzene, which has been either benzhydrylamidated, chloromethylated or hydroxymethylated to provide sites for amide or ester formation with the initially introduced amino protected amino acid.

An example of a hydroxymethyl resin is described by Bodansky *et al.* [*Chem. Ind.* (London) 38, 1597-98 (1966)]. The preparation of chloromethyl and benzhydrylamine resins are described by Stewart *et al.* ["Solid Phase Peptide Synthesis," 2nd Edition, Pierce Chemical Co., Rockford, Illinois (1984). Chapter 2, pp. 54-55]. Many of these resins are available commercially. In general, the amino protected amino acid which is desired on the carboxyl-terminal end of the peptide is bound to the resin using standard procedures and practices as are well known and appreciated in the art. For example, the amino protected amino acid can be bound to the resin by the procedure of Gisin [*Helv. Chem. Acta*, 56, 1476 (1973)]. When it is desired to use a resin containing a benzhydrylamine moiety as the resin binding site an amino protected amino acid is coupled to the resin through an amide linkage between the α-carboxylic acid and the amino moiety of the resin. The coupling is effected using standard coupling procedures as described below. Many resin-bound amino acids are available commercially.

The α-amino protecting group employed with each amino acid introduced into the polypeptide sequence may be any such protecting group known in the art. Among the classes of amino protecting groups contemplated are: (1) acyl type protecting groups such as formyl, trifluoroacetyl, phthalyl, p-toluenesulfonyl (tosyl), benzenesulfonyl, nitrophenylsulfonyl, tritylsulfonyl, o-nitrophenoxyacetyl, and α-chlorobutryl; (2) aromatic urethane type protecting groups such as benzyloxycarbonyl and substituted benzyloxycarbonyls such as p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, and benzhydryloxycarbonyl; (3) aliphatic urethane protecting groups such as t-butyloxycarbonyl (BOC), diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, and allyloxycarbonyl; (4) cycloalkyl

urethane type protecting groups such as cyclopentyloxycarbonyl, adamantyloxycarbonyl, and cyclohexyloxycarbonyl; (5) thiourethane type protecting groups such as phenylthiocarbonyl; (6) alkyl type protecting groups such as triphenylmethyl (trityl) and benzyl (Bn); and (7) trialkylsilane protecting groups such, but not limited to, as trimethylsilane, 4-[-(4-chlorophenyl) sulfonylaminocarbonyl] phenyl carbonyl, and 4-[-(4-bromophenyl) sulfonylaminocarbonyl] phenyl carbonyl. The preferred α-amino protecting group is t-butyloxycarbonyl (BOC); its use as an α-amino protecting group for amino acids is well known to those of skill in the art ([see, e.g., by Bodansky *et al.* in "The Practice of Peptide Synthesis," Springer-Verlag, Berlin (1984), p.20].

Following the coupling of the amino protected amino acid to the resin support, the α-amino protecting group may be removed using any suitable procedure such as by using trifluoroacetic acid, trifluoroacetic acid in CH_2Cl_2, or HCl in dioxane. The deprotection is carried out at a temperature of between 0° C and room temperature. Other standard cleaving reagents may be used for removal of specific amino protecting groups under conditions well known and appreciated in the art.

After removal and neutralization of the α-amino protecting group, the next desired amino-protected amino acid is coupled through a peptide linkage. This deprotection, neutralization and coupling procedure is repeated until a peptide of the desired sequence is obtained. Alternatively, multiple amino acid groups may be coupled by the solution method prior to coupling with the resin supported amino acid sequence.

The selection and use of an appropriate coupling reagent is within the skill of the skilled artisan. Particularly suitable coupling reagents where the amino acid to be added is Gln, Asn, or Arg include N,*N*-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole. The use of these reagents prevents nitrile and lactam formation. Other coupling agents are (1) other carbodiimides (e.g., *N*-ethyl-N'-(γ-dimethylaminopropylcarbo-

diimide); (2) ketenimines; (3) isoxazolium salts (e.g., *N*-ethyl-5-phenyl-isoxazolium-3-sulfonate); (4) monocyclic nitrogen-containing heterocyclic amides of aromatic character containing one through four nitrogens in the ring such as imidazolides, pyrazolides, and 1,2,4-triazolides (specific heterocyclic amides that are useful include N,*N*-carbonyldiimidazole and N,*N*-carbonyl-di-1,2,4-triazole); (5) alkoxylated acetylene (e.g., ethoxyacetylene); (6) reagents which form a mixed anhydride with the carboxyl moiety of the amino acid (e.g., ethyl chloroformate and *iso*-butyl chloroformate) or the symmetrical anhydride of the amino acid to be coupled (e.g., BOC-Ala-*O*-Ala-BOC); and (7) nitrogen-containing heterocyclic compounds having a hydroxyl group on one ring nitrogen (such as, but not limited to, *N*-hydroxyphthalimide, *N*-hydroxysuccinimide, and 1-hydroxybenzotriazole). Other activating reagents and their use in peptide coupling can be obtained and used as known in the art [see, Kapoor (1970) J. Pharm. Sci. 59:1-27]. Use of the symmetrical anhydride as the coupling agent is the generally preferred amino acid coupling method herein.

The preferred coupling method for Gln, Asn and Arg is to react the protected amino acid, or derivatives or isomers thereof, with N,*N*-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole (1:1) in DMF in the presence of the resin or resin-bound amino acid or peptide. The preferred coupling method for other amino acids involves reacting the protected amino acid, or derivative or isomer thereof, with N,*N*-dicyclohexylcarbodiimide in CH_2Cl_2 to form the symmetrical anhydride. The symmetrical anhydride is then introduced into the solid phase reactor containing the resin or resin-bound amino acid or peptide, and the coupling is carried out in a medium of DMF, or CH_2Cl_2, or DMF: CH_2Cl_2 (1:1). A medium of DMF is preferred. The success of the coupling reaction at each stage of the synthesis is monitored by a ninhydrin test as described by Kaiser *et al.* [*Analyt. Biochem.* 34, 595 (1970)]. In cases

where incomplete coupling occurs, the coupling procedure is repeated. If the coupling is still incomplete, the deprotected amine is capped with a suitable capping reagent to prevent its continued synthesis. Suitable capping reagents and the use thereof are well known and appreciated in the art. Examples of suitable capping reagents are acetic anhydride and acetylimidazole as described by Stewart *et al.* ["Solid Phase Peptide Synthesis," 2nd Ed., Pierce Chemical Co., Rockford, Ill. (1984), Chapter 2, p.73].

After the desired amino acid sequence has been obtained, the peptide is cleaved from the resin. This can be effected by procedures which are well known and appreciated in the art, such as by hydrolysis of the ester or amide linkage to the resin. It is preferred to cleave the peptide from the benzhydrylamine resin with a solution of dimethyl sulfide, p-cresol, thiocresol, or anisole in anhydrous hydrogen fluoride. The cleavage reaction is preferably carried out at temperatures between about 0°C and about room temperature, and is allowed to continue preferably from between about 5 minutes to about 5 hours.

As is known in the art of solid phase peptide synthesis, many of the amino acids bear side chain functionalities requiring protection during the preparation of the peptide. The selection and use of an appropriate protecting group for these side chain functionalities is within the ability of those skilled in the art and will depend upon the amino acid to be protected and the presence of other protected amino acid residues in the peptide. The selection of such a side chain protection group is critical in that it must not be removed during the deprotection and coupling steps of the synthesis. For example, when BOC is used as the α-amino protecting group, the following side chain protecting groups are suitable: p-toluenesulfonyl (tosyl) moieties can be used to protect the amino side chains of amino acids such as Lys and Arg; p-methylbenzyl, acetamidomethyl, benzyl (Bn), or t-butylsulfonyl moieties can be used to

protect the sulfide-containing side chains of amino acids such as cysteine, homocysteine, penicillamine and the like or derivatives thereof; benzyl or cyclohexyl ester moieties can be used to protect carboxylic acid side chains of amino acids such as Asp, Glu; a benzyl ether can be used to protect the hydroxyl-containing side chains of amino acids such as Ser and Thr; and a 2-bromocarbobenzoxy (2Br-Cbz) moiety can be used to protect the hydroxyl-containing side chains of amino acids such as Tyr. These side chain protecting groups are added and removed according to standard practices and procedures well known in the art. It is preferred to deprotect these side chain protecting groups with a solution of anisole in anhydrous hydrogen fluoride (1:10). Typically, deprotection of side chain protecting groups is performed after the peptide chain synthesis is complete but these groups can alternatively be removed at any other appropriate time. It is preferred to deprotect these side chains at the same time as the peptide is cleaved from the resin.

The compounds are then isolated and purified by standard techniques. The desired amino acids, derivatives and isomers thereof can be obtained commercially or can be synthesized according to standard practices and procedures well known in the art.

C. Identification of preferred compounds using assays that identify compounds that modulate processing of amyloid precursor protein (APP) or that modulate other selected processing pathways

Compounds provided herein modulate the processing of proteins, such as amyloid precursor protein (APP), involved in diseases. Particular compounds may be selected for treatment of a particular disorder empirically using in vitro or in vivo animal models, such as those that were used to identify the ketones and aldehyde compounds that correspond to the alcohols provided herein.

For example, among the compounds provided herein are those that modulate processing of APP. This modulation can be demonstrated in a

variety of ways. For example, compounds can be evaluated for the ability to modulate generation of Aβ or α-sAPP.

1. In vitro assays

The compounds provided herein yield a positive result in one or more in vitro assays that assess the effects of test compounds on processing of APP. In particular, in vitro assay systems for identifying such compounds are provided herein. These assays evaluate the effects of a test compound on processing of APP and use cultured human glioblastoma cell lines that have been transfected with DNA encoding either a wild-type 695 amino acid isoform of APP or a mutein of the 695 amino acid form of APP that contains changes (in this case two or three amino acid changes have been made) that appear to make the molecule more susceptible to proteolytic cleavage that results in increased production of Aβ [see, e.g., Mullan et al. (1992) Nature Genet. 1:345-347].

In performing these assays, a test compound is added to the culture medium and, after a selected period of time, the culture medium and/or cell lysates are analyzed using immunochemical assays to detect the relative amounts of Aβ, total soluble APP (sAPP), a portion of sAPP designated α-sAPP, and C-terminal fragments of APP. In particular, the culture medium and cell lysates are analyzed by immunoblotting coupled with laser scanning densitometry and ELISAs using several different antibodies. A positive test, occurs when: (1) there is a decrease in the ~4-kDa amyloid β-protein (Aβ) in the medium relative to control cultures (4-kDa assay); and/or (2) the relative amount of total sAPP in the medium increases (e.g., relative to the amount of total sAPP in medium from appropriate control cells such as cells not exposed to test compound); and/or (3) there is a decrease in the amount of C-terminal amyloidogenic fragments larger than 9 kDa and smaller than 22 kDa in the cell lysate as a result of differential processing; and/or (4) there is an increase in the

amount of α-sAPP in the medium relative to control cultures. Control cultures can be cultures that have not been contacted with the compound. The Aβ assay is done using cells (e.g., HGB 717/Swed) that have been transfected with DNA encoding the mutein APP; the other assays are performed using cells, such as HGB695 cells, that have been transfected with DNA encoding a wild-type APP.

Preferred compounds have activity that is at least 2-fold, preferably 5-fold, more preferably 10-fold, most preferably 50-100-fold, greater activity than *N*-Acetylleucylleucylnorleucinal [see, e.g., EP 0 504 938 A2; and Sherwood et al. (1993) Proc. Natl. Acad. Sci. U.S.A. 90:3353-3357] in at least one, preferably the Aβ assay, of these assays.

2. The amount of α-sAPP and the ratio of α-sAPP to total sAPP in cerebrospinal fluid (CSF) as an indicator of Alzheimer's Disease (AD) and the effectiveness of therapeutic intervention

The relative amount of α-sAPP and the ratio of α-sAPP to total sAPP in CSF are shown herein to be useful markers in the detection of neurodegenerative disorders characterized by cerebral deposition of amyloid (e.g., AD) and in monitoring the progression of such disease. Furthermore, assay systems incorporating these markers can be used in monitoring therapeutic intervention of these diseases.

The amount of α-sAPP and the ratio of α-sAPP to total sAPP in CSF samples can be used as an indicator of Alzheimer's Disease and other neurodegenerative disorders. For purposes herein, this amount and/or the ratio can also be used to assess the effectiveness of compounds provided herein in treating Alzheimer's Disease and neurodegenerative disorders.

It has been found that patients with suspected Alzheimer's disease (as diagnosed by other indicia, or confirmed by autopsy) have a statistically significant lower ratio of α-sAPP to total sAPP in CSF and also have statistically significant lower levels of α-sAPP. Therefore, by comparison with non-Alzheimer's disease controls or by existence of a

ratio lower than a predetermined standard, based, for example, on averages in samples from large numbers of unafflicted individuals, or an amount of α-sAPP lower than a predetermined standard, Alzheimer's disease or, depending upon other indications, another neurodegenerative disease is indicated.

Compounds, such as those provided herein, that alter this ratio or the level of α-sAPP closer to that of individuals who do not have a neurodegenerative disorder characterized by the cerebral deposition of amyloid are considered useful for treating these disorders.

3. In vivo assays

The ability of compounds to modulate processing of APP can also be evaluated in vivo [see, e.g., Kowall et al. (1991) Proc. Natl. Acad. Sci. U.S.A. 88:7247-7251]. Compounds can be administered through a canula implanted in the cranium of a rodent or other suitable test animal [see, e.g., Lamb et al. (1993) Nature Genet. 5:22-29; Pearson et al. (1993) Proc. Natl. Acad. Sci. U.S.A. 90:10578-10582]. After a predetermined period of administration the rodents are sacrificed. Selected brain regions, e.g., hippocampi, or CSF are evaluated in immunoblot assays or other suitable assays to determine the relative level of α-sAPP, or the ratio of α-sAPP to total sAPP, and amyloidogenic C-terminal fragments of APP compared to untreated control animals. Compounds that result in relative increases in the amount and/or ratio of α-sAPP are selected, as are those which decrease the amount of amyloidogenic C-terminal fragments of APP.

D. Formulation of pharmaceutical compositions

Compositions are provided that contain therapeutically effective amounts of the compounds of formulae (I), (II) and (III). The compounds are preferably formulated into suitable pharmaceutical preparations such as tablets, capsules or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch

preparation. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art.

About 10 to 500 mg of a compound or mixture of compounds for Formulae (I), (II) and (III) or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in those compositions or preparations is such that a suitable dosage in the range indicated is obtained.

To prepare compositions, one or more compounds of formulae (I), (II) and (III) are mixed with a suitable pharmaceutically acceptable carrier. Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. Liposomal suspensions may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action or have other action. The compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients.

In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as tween, Creamaphor (Sigma Chemical Company) or polyethylene glycol/ethanol solution (80% v/v:20% v/v) or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as salts of the compounds or prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

The concentrations of the compounds are that effective for delivery of an amount, upon administration, that ameliorates the symptoms of the disorder for which the compounds are administered. Typically, the compositions are formulated for single dosage administration.

The compounds of formulae (I), (II) and (III) may be prepared with carriers that protect them against rapid elimination from the body, such as time release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, microencapsulated delivery systems.

The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in known in vitro and in vivo model systems for the treated disorder.

The compositions can be enclosed in ampules, disposable syringes or multiple or single dose vials made of glass, plastic or other suitable material. Such enclosed compositions can be provided in kits.

The concentration of active compound in the drug composition will depend on absorption, inactivation and excretion rates of the active

compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

If oral administration is desired, the compound should be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

Oral compositions will generally include an inert diluent or an edible carrier and may be compressed into tablets or enclosed in gelatin capsules. For the purpose of oral therapeutic administration, the active compound or compounds can be incorporated with excipients and used in the form of tablets, capsules or troches. Pharmaceutically compatible binding agents and adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder,

such as, but not limited to, gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose, starch and lactose, a disintegrating agent such as, but not limited to, alginic acid and corn starch; a lubricant such as, but not limited to, magnesium stearate; a glidant, such as, but not limited to, colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and a flavoring agent such as peppermint, methyl salicylate, and fruit flavoring.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc. or a synthetic fatty vehicle like ethyl oleate or the like, polyethylene glycol, glycerine, propylene glycol or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral

preparations can be enclosed in ampules, disposable syringes or multiple dose vials made of glass, plastic or other suitable material. Buffers, preservatives, antioxidants and the like can be incorporated as required.

If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof. Liposomal suspensions, including tissue-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as described in U.S. Patent No. 4,522,811.

The active compounds may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of such formulations are known to those skilled in the art.

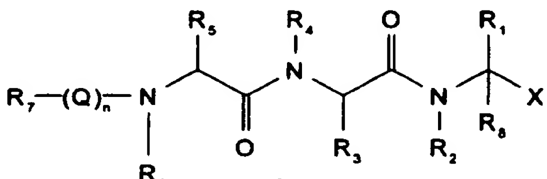
The compounds may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Such solutions, may be formulated as 0.01% - 100% (weight to volume) isotonic solutions, pH about 5-7, with appropriate salts. The compounds may be formulated as aeorsols for topical application, such as by inhalation [see, e.g., U.S. Patent Nos. 4,044,126, 4,414,209, and 4,364,923].

Finally, the compounds may be packaged as articles of manufacture containing packaging material, an acceptable composition containing a compound of formulae (I), (II) and (III) provided herein, which

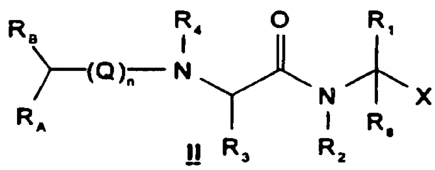
is effective for treating the particular disorder, and a label that indicates that the compound or salt thereof is used for treating the disorder.

E. Methods of use

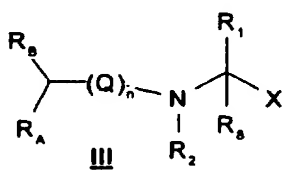
The compounds for use in the methods herein have the formulae (I), (II) and (III):



I



II



III

or the hydrates and isosteres, diastereomeric isomers and mixtures thereof, or pharmaceutically acceptable salts thereof in which X is selected as described above, and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi) or (vii), as described above.

These compounds have pharmacological utility and also utility as reagents. It is recognized in this art that compounds that exhibit activity as protease inhibitors have use for the treatments of particular disorders in which particular proteases are implicated. For example compounds that exhibit activities in assays that assess the ability of the compounds to alter or modulate the activity of proteins associated with the deposition of cerebral amyloid, are pharmacologically useful and potentially

therapeutically useful in the treatment of disorders that involve such deposition.

The dose ranges, which can be established empirically, for use in the treatment of disease states will depend upon the etiology, nature, and severity of the disease state as well as such other factors as determined by the attending physician. The broad range for effective treatment is about 0.01 to 10 mg per kilogram (kg) of body weight per day. The preferred range is about 0.1 to 10 mg/kg of body weight per day.

Included among the compounds for use in the methods here in are those that are alcohols, preferably secondary alcohols, that correspond to peptidyl or petidyl analog ketone protease inhibitors [see, e.g., Skiles et al. (1992) J. Med. Chem. 35:641-662; Mjali et al. (1994) Bioorg. Med. CHem. Lttrs. 4:1965-1968; Imperiali et al. (1986) Biochem. 25:3760-3767; Angelastro et al. (1994) J. Med. Chem. 37:4538-4554; published European patent application EP 0 410 411 A2]. Other compounds are those of formulae (I), (II) and (III).

The active compounds can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration. Preferred modes of administration include oral and parenteral modes of administration.

Since, it is feasible to measure the presence of, and over the course of time, to determine the rate of increase of those protein segments believed to be a critical factor influencing the formation of amyloid plaques located in the brain (see, e.g., U.S. Patent No. 5,270,165 and the CSF assay provided herein and described above and in the EXAMPLES), dosages can be empirically determined by the physician. As these techniques involve the use of cerebrospinal fluids, such techniques and other equivalently functioning procedures, will be

useful to the attending physician in determining the need to modify the dosage for individual patients.

In treating these disease states, it is sufficient to start treating the patient as soon as the attending physician makes a diagnosis that the patient is suffering from one of these diseases. Thus, although the progress of treatment of the patient may be monitored by the measurements of those biological factors which characterize the diseases, it is not necessary to so-evaluate such characteristics before treatment. Rather it is within the provence of the attending physician to determine when it is in the best interest of the patient to start treatment. Therefore, patients showing increased probabilities of the disease state, (e.g. by carrying known familial genetic markers that increase the probability of the incidence of neurodegenerative diseases as well as the patient's general behavioral characteristics and other indicia of these diseases) can be treated by the methods and with the compositions provided herein.

1. Treatment of neurodegenerative diseases

Amyloid plaques are believed to accompany and/or to be involved in the process responsible for the development and progression of certain neurodegenerative disease states. Without being bound by any theory of action, it is believed that the compounds provided herein modulate the generation of amyloidogenic peptides to effectuate a beneficial result. Without any intent to limit -or restrict- the compounds and methods provided herein to any specific mechanism of action for the end-use applications, it is believed that the compounds effectuate a modulation of the processing of the amyloid precursor protein (APP), the progenitor of the deposited amyloidogenic Aβ peptides (39 to 43 amino acid residues) found in senile plaques in the brains of patients diagnosed with, for example, Alzheimer's disease. Thus, the compounds provided herein are useful in the treatment of such neurodegenerative disease states in which

such amyloid plaques accumulate or are implicated in the etiology thereof, including, but not limited to: Alzheimer's disease, cognition deficits, Down's Syndrome, Parkinson's disease, cerebral hemorrhage with amyloidosis, dementia pugilistica, head trauma and in the treatment of conditions characterized by a degradation of the neuronal cytoskeleton resulting from a thrombolytic or hemorrhagic stroke.

For example, it is believed that the compounds can be used in the treatment of Alzheimer's patients through the modulation of APP processing to effectuate a beneficial result by: (a) decreasing the formation of Aβ; (b) modulating the generation of a mutually exclusive, alternative-processed form of APP that precludes Aβ formation (α-sAPP); and/or, (c) modulating the generation of partially processed C-terminal Aβ-containing amyloidogenic peptides.

In addition, these compounds may also beneficially modulate neurodegenerative abnormalities not thought to be associated with amyloid plaques, such as stroke, by beneficially affecting the rate of degeneration of the neuronal cytoskeleton that occurs as a result of thrombolytic or hemorrhagic stroke.

It is believed that the treatment of patients with such disorders with these compounds will result in a beneficial modulation of the symptoms of or causative factors involved in neurodegenerative disease states and will result in an enhanced lifestyle as well as to delay or obviate the need to institutionalize these patients.

The compounds can be administered to patients in need of such treatment in a dosage range of 0.01-10 mg per kg of body weight per day. and can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration. As stated above, the

dose will vary depending on severity of disease, weight of patient and other factors which a person skilled in the art will recognize.

Patients include those with a neurodegenerative disease, including but not limited to Alzheimer's disease, cognition deficits, Down's Syndrome, Parkinson's disease, cerebral hemorrhage with amyloidosis, dementia pugilistica, and head trauma. Treatment is effected by administering to such patient a therapeutically effective amount of a compound of the formulae (I), (II) and (III) defined as above. Particularly preferred for use in these methods are the compounds particularly provided herein, including the compounds of formulae (I), (II) and (III) as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid and X is a tertiary or secondary haloalkyl alcohol, R_1 is not the side chain of cyclohexylalanine or cyclohexylglycine.

In other embodiments, the methods use compounds that have formula (III), as defined above, then, when X is a tertiary or secondary haloalkyl alcohol, R_1 is the side chain of a non-naturally-occurring α-amino acid and it is not the side chain of cyclohexylalanine or cyclohexylglycine.

In certain other embodiments, the methods use compounds that have formulae (I) or (II), as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, R_1 is not the side chain of cyclohexylalanine or cyclohexylglycine.

In certain other embodiments, the methods use compounds that have formulae (I), (II) or (III) as defined above, but with the proviso that,

when the compounds have formula (I) or (II): R_1 is a side chain of a non-naturally-occurring amino acid, the side chain of R_1 is of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, unless the compounds are primary alcohols, then the non-naturally-occurring amino acid is other than norleucine or norvaline.

Thus, in certain other embodiments the methods use compounds that are primary alcohols, when the compounds are primary alcohols, they have formulae (I) or (II), particularly formula I, as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, it is not the side chain of norleucine or norvaline.

Thus, in certain other embodiments in which the compounds used in the methods are primary alcohols, the compounds have formulae (I) or (II), particularly formula I, as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, it is not the side chain of cyclohexylalanine, cyclohexylglycine, norleucine or norvaline.

In other embodiments, the methods use compouds that have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine or norvaline.

In other embodiments, the methods use compouds that have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I), (II) or (III): R_1 is a side chain of a non-

naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine or norvaline.

In other embodiments, the methods use compounds that have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine, norvaline, citrulline, ornithine, 4-phenyl-2-aminobutyric acid, 1-naphthylalanine, 2-naphthylalanine, sarcosine, 2-indolinecarboxylic acid, *β*-alanine, *β*-valine, *N*-6-acetyllysine, O-4'-methyltyrosine, a substituted alanine and guanidinophenylalanine.

In other embodiments, the methods use compounds that have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I), (II) or (III): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine, norvaline, citrulline, ornithine, 4-phenyl-2-aminobutyric acid, 1-naphthylalanine, 2-naphthylalanine, sarcosine, 2-indolinecarboxylic acid, *β*-alanine, *β*-valine, *N*-6-acetyllysine, O-4'-methyltyrosine, a substituted alanine and guanidinophenylalanine.

In certain other embodiments, the methods use compounds that have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): at least one of the amino acid residues in the resulting di-peptide or tri-peptide is a non-naturally-occurring *α*-amino acid or at least one of the R_1, R_3 and R_5, preferably R_1, is a side chain of a non-naturally-occurring amino acid, R_1 is not cyclohexylalanine, and the at least one non-naturally occurring amino acid (or side chain thereof) is other than norleucine or norvaline, unless the resulting residue is a halo-substituted alcohol, particularly fluoro-substituted alcohols. Such compounds include, but are not limited to: (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-

(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide and (2SR)-(3SR)-*N*-valeroyl-L-Leu *N*-[3-(1 ,1,1-trifluoro-2-heptanol)]amide.

In other embodiments, the methods use compounds that have formulae (I) or (II) and at least one of R_1, R_3 and R_5, preferably R_1 or R_5, includes at least one unsaturated bond so that at least one of R_1, R_3 and R_5, preferably R_1 and R_5, is a straight or branched carbon chain containing at least one unsaturated bond, preferably a double bond, and 2 to 10, preferably 3 to 7, more preferably 4 to 6, carbon atoms in the chain. Such side chains include, but are not limited to substituted and unsubstituted propenes, butenes, pentenes, such as, 2-methyl-propenyl and 2-butenyl, which are among the preferred residues.

2. Treatment of diseases characterized by degeneration of the cytoskeleton

Also provided are methods of treating a patient suffering from a disease state characterized by the degeneration of the cytoskeleton arising from a thrombolytic or hemorrhagic stroke by administering a therapeutically effective amount of a compound of the formulae (I), (II) or (III) defined as above.

Particularly preferred for use in these methods are the compounds particularly provided herein, including the compounds of formulae (I), (II) and (III) as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid and X is a tertiary or secondary haloalkyl alcohol, R_1 is not the side chain of cyclohexylalanine or cyclohexylglycine.

In other embodiments, the methods use compounds that have formula (III), as defined above, then, when X is a tertiary or secondary haloalkyl alcohol, R_1 is the side chain of a non-naturally-occurring α-amino

acid and it is not the side chain of cyclohexylalanine or cyclohexylglycine.

In certain other embodiments, the methods use compounds that have formulae (I) or (II), as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, R_1 is not the side chain of cyclohexylalanine or cyclohexylglycine.

In certain other embodiments, the methods use compounds that have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): R_1 is a sidechain of a non-naturally-occurring amino acid, the side chain of R_1 is of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, unless the compounds are primary alcohols, then the non-naturally-occurring amino acid is other than norleucine or norvaline.

Thus, in certain other embodiments the methods use compounds that are primary alcohols, when the compounds are primary alcohols, they have formulae (I) or (II), particularly formula I, as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid, it is not the side chain of norleucine or norvaline.

Thus, in certain other embodiments in which the compounds used in the methods are primary alcohols, the compounds have formulae (I) or (II), particularly formula I, as defined above, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is

the side chain from a non-naturally occurring amino acid, it is not the side chain of cyclohexylalanine, cyclohexylglycine, norleucine or norvaline.

In other embodiments, the methods use compounds that have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine or norvaline.

In other embodiments, the methods use compounds that have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I), (II) or (III): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine or norvaline.

In other embodiments, the methods use compounds that have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I) or (II): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine, norvaline, citrulline, ornithine, 4-phenyl-2-aminobutyric acid, 1-naphthylalanine, 2-naphthylalanine, sarcosine, 2-indolinecarboxylic acid, *β*-alanine, *β*-valine, *N*-6-acetyllysine, O-4'-methyltyrosine, a substituted alanine and guanidinophenylalanine.

In other embodiments, the methods use compounds that have formulae (I), (II) or (III) as defined above, but with the proviso that, when the compounds have formula (I), (II) or (III): R_1 is a side chain of a non-naturally-occurring amino acid other than cyclohexylalanine or cyclohexylglycine, norleucine, norvaline, citrulline, ornithine, 4-phenyl-2-aminobutyric acid, 1-naphthylalanine, 2-naphthylalanine, sarcosine, 2-indolinecarboxylic acid, *β*-alanine, *β*-valine, *N*-6-acetyllysine, O-4'-methyltyrosine, a substituted alanine and guanidinophenylalanine.

In certain other embodiments, the methods use compounds that have formulae (I), (II) or (III) as defined above, but with the proviso that,

when the compounds have formula (I) or (II): at least one of the amino acid residues in the resulting di-peptide or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5, preferably R_1, is a side chain of a non-naturally-occurring amino acid, R_1 is not cyclohexylalanine, and the at least one non-naturally occurring amino acid (or side chain thereof) is other than norleucine or norvaline, unless the resulting residue is a halo-substituted alcohol, particularly fluoro-substituted alcohols. Such compounds include, but are not limited to: (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide and (2SR)-(3SR)-*N*-valeroyl-L-Leu *N*-[3-(1 ,1,1-trifluoro-2-heptanol)]amide.

In other embodiments, the methods use compounds that have formulae (I) or (II) and at least one of R_1, R_3 and R_5, preferably R_1 or R_5, includes at least one unsaturated bond so that at least one of R_1, R_3 and R_5, preferably R_1 and R_5, is a straight or branched carbon chain containing at least one unsaturated bond, preferably a double bond, and 2 to 10, preferably 3 to 7, more preferably 4 to 6, carbon atoms in the chain. Such side chains include, but are not limited to substituted and unsubstituted propenes, butenes, pentenes, such as, 2-methyl-propenyl and 2-butenyl, which among the preferred residues.

3. Protease inhibition in cells

The compounds provided herein have activity as inhibitors of cellular proteases, such as cysteine proteases, including calpain . It is believed by those of skill in this art that excessive activation of the Ca^{2+}-dependent protease calpain plays a role in the pathology of a variety of disorders, including cerebral ischaemia, cataract, myocardial ischaemia, muscular dystrophy and platelet aggregation. Thus, compounds that have activity as calpain inhibitors are considered by those of skill in this art to be useful [see, e.g., U.S. Patent No. 5,081,284, Sherwood et al.

(1993) Proc. Natl. Acad. Sci. U.S.A. 90:3353-3357]. Assays that measure the anti-calpain activity of selected compounds are known to those of skill in the art (see, e.g., U.S. Patent No. 5,081,284). Activities of inhibitors in such in vitro assays at concentrations [IC_{50}] in the nanomolar range or lower are indicative of therapeutic activity. Such compounds also have utility in the purification of proteinases, such as cysteine proteases, on affinity columns of these compounds (see, U.S. Patent No. 5,081,284). Also, calpain inhibitors, such as *N*-Acetylleucylleucylnorleucinal [see, e.g., EP 0 504 938 A2; and Sherwood et al. (1993) Proc. Natl. Acad. Sci. U.S.A. 90:3353-3357], which is commercially available, are used as reagents in the study of protein trafficking and other cellular processes [see, e.g., Sharma et al. (1992) J. Biol. Chem. 267:5731-5734]. Finally, inhibitors of cysteine proteases strongly inhibit the growth of *Plasmodium falciparum* and *Schistosoma mansoni* [see, e.g., Scheibel et al. (1984) Protease inhibitors and antimalarial effects. In: Malaria and the Red Cell, Progress in CLinical and Biological Research, Alan R. Liss, Inc., NY, pp. 131-142]. Thus, the compounds herein may be used as such reagents or to inhibit the growth of certain parasites.

The methods of protease inhibition in cells may employ any of the compounds of formulae (I), (II) and (III) or peptidyl, peptidyl analog and amino acid analog alcohols, particularly haloalkyl secondary alcohols that are the corresponding alcohols of any peptidyl or peptidyl analog ketones or aldehydes that inhibit proteases in cell-free assays [see, EP 0 410 411 A2, which is based on U.S. application Serial No. 07/385,624, WO 92/20357, which is based on U.S. application Serial No. 08/704,449, EP 0 364 344 A2, which is based on U.S. application Serial No. 08/254,762]. In practicing these methods, cells are contacted with the compound. Compounds that have specificity for a particular protease may be selected by contacting the compounds with cells that produce

compounds processed by such protease or that express such protease. Compounds that result in a decrease in such processing or protease activity are selected. The APP processing assay set forth herein is exemplary of such cell-based assays.

4. Identification and/or isolation of proteases

The protease inhibitory activity of compounds provided herein makes such compounds amenable for use in identification and/or isolation of proteases with which the compounds interact. Using standard protein purification techniques known in the art [see e.g., Nicholson et al. Nature 376:37-43 (1995)], the compounds can be used as affinity ligands in isolation of proteases. For example, a compound may be linked to a support, such as activated agarose, CNBr Sepharose, streptavidin agarose or resin such as Affi-gel, covalently or by other linkage, through the R_7-$(Q)_n$ or (R_B)-$CH(R_A)$-$(Q)_n$- moieties. In coupling the compound to the support in this manner, the remainder of the compound molecule remains available to interact with protease proteins contained in a sample passed through a column containing the compound-coupled support material. The resin is preequilibrated with a suitable buffer prior to adding the composition containing the protease to be isolated, i.e., typically a cell lysate. Interaction of the immobilized compound and protease effects separation of the protease from the other constitutents of the lysate which is followed by subsequent isolation of the protease through elution from the column. Preparation of the cell lysate and resin and elution of the column may be performed by modification of standard protocols known to those of skill in the art.

Compounds particularly intended for use in isolation of proteins, such as specific proteases, are those displaying the most significant activity in modulating the processing of APP (determined, for example, as described in Example 31 to identify compounds with activity at lower concentrations, e.g., $IC_{50} < 50\ \mu M$). These compounds may be used in

isolating proteins such as secretases, including β and gamma secretases, which may be involved in generating fragments of APP. β and gamma secretase refer to the activities associated with the cleavage of APP that gives rise to the Aβ peptide.

Compounds provided herein in which the R_7-$(Q)_n$ or (R_B)-$CH(R_A)$-$(Q)_n$- moiety is a chemical labeling/linking group are also useful in isolating and/or detecting proteases. The labeling groups contain chemical linkers whereby the label portion of the group is directly attached to the peptide compounds through the nitrogen of formulae I and II that is linked to $(Q)_n$. [See Nicholson et al., supra, for an exemplary methods of linking a chemical labeling group to a peptide.] Chemical labels are well known to those skilled in the art. Biotin, a commonly used chemical label, bonded to caproic acid is an example of one such chemical labeling group incorporated into compounds of formulae I and II as R_7-$(Q)_n$ or (R_B)-$CH(R_A)$-$(Q)_n$-. Compounds containing a biotin label can be used to detect proteases with which they interact in a sample (e.g., a cell lysate or a fraction thereof) containing the protease. The compound-protease complex is detected by exposing the sample to a biotin binding partner, such as steptavidin, which in turn is bound to a signal-generating moiety such as horse radish peroxidase (HRP). Addition of peroxidase to the sample yields a signal detected spectrophotometrically. A biotin labeled compound provided herein can also be used to isolate proteases that interact with the compound. For example, the compound can be bound to a a steptavidin-agarose resin and used as an affinity resin. Additionally, compounds in which the R_7-$(Q)_n$ or (R_B)-$CH(R_A)$-$(Q)_n$- moiety is a chemical linking group are also useful in isolating proteases through direct coupling of the compound to a resin through, e.g., a primary amine of the linking group. Preferred linking groups include 6-amino caproic acid and amino decanoic acid.

5. Identification of protease inhibitors and modulators of APP processing

The compounds provided herein as chromogenic or fluogenic substrates wherein X is a chromophore or fluorophore are useful in identifying protease inhibitors. These compounds are readily prepared by using methods of synthesizing peptides of formulae I, II and III as described herein (see, for example, reaction schemes A-N and Examples 1-30). For example, to prepare a chromogenic substrate, the appropriate protected amino acid moiety (e.g., compound A-1 in Scheme A) in N-methyl morpholine is coupled to *p*-nitraniline (Aldrich Chemical Co.) at about 0° C in the presence of isobutyl chloroformate in an aprotic solvent (e.g., THF) under an inert atmosphere by stirring for 12-24 hr, preferably 12 hr. The product is purified by chromatography and deptroteced by hydrolysis in 4 N HCl in dioxane. Following their preparation, the P_1 moieties are coupled (e.g. via EDC methods described herein in the reaction schemes) with the appropriate P_2P_3 moiety (e.g., compound A-4 in Reaction Scheme A), or with the appropriate P_2 moiety (e.g., compound J-5 in Reaction Scheme J) to produce the chromogenic substrates of formula (I) and (II).

Fluorogenic substrates wherein X is 7-amino-4-methylcoumarin (AMC) may be prepared, for example, as follows. The appropriate protected amino acid moiety (e.g., compound A-1 in Reaction Scheme A) in N-methyl morpholine is coupled to 7-amino-6-methylcoumarin (Aldrich Chemical Co.) at about -15° C in the presence of iso-butyl chloroformate in an aprotic solvent (e.g., THF) under an inert atmosphere by stirring for 12-24 hr, preferably 12 hr. The product is purified by chromatography and deprotected by hydrolysis in 4 N HCl in dioxane. Following their preparation, the P_1 moieties are coupled (e.g. via EDC methods described herein in the reaction schemes) with the appropriate P_2P_3 moiety (e.g., compound A-4 in Reaction Scheme A), or with the appropriate P_2 moiety

(e.g., compound J-5 in Reaction Scheme J) to produce the fluorogenic substrates of formula (I) and (II).

In addition, the resulting compounds may be deprotected by hydrolysis in 4 NHCl in dioxane and coupled with succinic acid, decanoic acid or 6-amino caproic acid thereby generating a free carboxylate or amino group at the amino terminus for coupling the compounds to a solid resin support (e.g., cyanogen bromide-conjugated Sepharose) for identification and isolation of proteases.

To use the fluorogenic and chromogenic substrates in methods of identifying protease inhibitors, the substrates are incubated, in the presence and absence of test compound, with a selected purified protease (or a cell lysate fraction enriched for the protease activity) in a suitable buffer for optimum protease activity (e.g., 100 μl of 0.1 M potassium phosphate buffer, pH 7.5, supplemented with 5 mM DTT and 5 mM EDTA). Cleavage of the substrate by the protease liberates the fluophore or chromophore. Test compounds that inhibit this cleavage are those of interest.

The liberated chromophores or fluophores can be readily detected. For example, fluorescence of the freed fluophore may be detected using standard fluorometry by applying excitation radiation of the appropriate wavelength for the particular fluophore used (e.g., 360 nm for AMC) followed by measurement of the resulting emitted radiation of a different wavelength (e.g., 460 nm for AMC). [For further details of fluorescence detection of fluophores see Kirschke and Wiederanders (1995) Meth. Enzymol. 244:500-511.] Likewise, color emitted by a released chromophore may be detected using a spectrophotometer and standard procedures (e.g., detection of free nitroanilide at 405 nm).

Test compounds that inhibit fluorescence or color emission resulting from cleavage of the substrate by proteases may be potential inhibitors of the protease. The protease inhibitor identification methods

using the chromogenic and fluorogenic substrates provide rapid, cell-free assays amenable to high through-put procedures for screening large numbers of test compounds and identifying compounds that are candidate inhibitors.

Compounds that are positive in the protease inhibitor assay may be further characterized using any of the assay systems described herein. For example, when a compound is positive in an assay employing a fraction enriched for APP-processing activity, it may be further evaluated in assays described as in Example 31 for identifying compounds having activity as modulators of APP processing.

The following specific examples further illustrate the methods by which compounds of formulae (I), (II) and (III) may be prepared, but are not meant to limit the scope of this invention to the specific compounds. Thus, the following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

EXAMPLE 1

Preparation of L-(methyl)Nle methyl ester hydrochloride

To a stirred solution of the *N*-BOC-L-Nle methyl ester [1.0 eq] in 20:1 anhydrous tetrahydrofuran:dimethylformamide [THF:DMF] at 0° C under Argon [Ar] is added methyl iodide [2.0 eq] and 60% sodium hydride [NaH] in oil dispersion [1.1 eq]. The reaction mixture is refluxed for 16 h. The mixture is poured onto 10% aqueous hydrogen chloride [10% HCl] and is extracted with ethyl acetate [EA]. The combined organic extract is washed with saturated aqueous sodium chloride [sat. NaCl], dried over magnesium sulfate [$MgSO_4$], filtered and concentrated *in vacuo* to afford *N*-BOC-L-(methyl)Nle methyl ester.

N-BOC-L-(methyl)Nle methyl ester [1.0 eq] is treated with 4 N hydrogen chloride [4 N HCl] in dioxane at room temperature [R.T.]. The reaction mixture is stirred for 1.5 h then concentrated *in vacuo*. The solid

is treated with anhydrous ether and concentrated *in vacuo*. The resulting L-(methyl)Nle methyl ester hydrochloride is isolated.

EXAMPLE 2

Preparation of the precusor ethyl 2-amino-4-methyl-4-pentenoate hydrochloride

To a solution of *N*-(diphenylmethylene)glycine ethyl ester [6.6 g, 24.7 mmol] in anhydrous THF at -78° C under Ar was slowly added 1.0 M lithium bis(trimethylsilyl)amide [LiHMDSi] in THF [24.7 mL, 24.7 mmol] over a 15 min time period. Stirring was continued for 30 min at -78° C, then 3-bromo-2-methylpropene [2.5 mL, 25.0 mmol] was added. The mixture was gradually warmed to R.T. then stirred for 1 h at R.T. The reaction mixture was treated with water [H_2O] and then concentrated. The residue was taken up in EA [50 mL]. The organic layer was washed with saturated aqueous sodium chloride [sat. NaCl; 2 x 10 mL], dried [$MgSO_4$], filtered and concentrated. The crude was purified by flash chromatography on silica gel [(ethyl acetate:hexane (EA:H); 1:4] to give ethyl 4-methyl-2-[(diphenylmethylene)amine]-4-pentenoate as a colorless oil [6.4 g, 89.3%]: ^{1}H NMR [$CDCl_3$, 300 MHz] δ 1.23 - 1.29 [t, 3 H, J = 6.0 Hz], 1.48 - 1.49 [m, 3 H], 2.55 - 2.69 [m, 2 H]. 4.11 - 4.24 [m, 3 H], 4.71 - 4.75 [m, 2 H], 7.16 - 7.83 [m, 10 H] ppm.

To a stirred solution of the above ethyl ester [6.4 g, 20.0 mmol] in anhydrous ether [15 mL] at R.T. was added 1 N aqueous hydrogen chloride [1 N HCl ;70 mL]. After 40 min, the two phases were separated, and the aqueous layer was washed with ether [3 x 10 mL]. The aqueous layer was adjusted with 1 N aqueous sodium hydroxide [1 N NaOH; pH = 10], then extracted with ether [3 x 20 mL]. The combined organic extrâcts is dried [$MgSO_4$], filtered and then adjusted with 4 N HCl/dioxane [pH 3] and concentrated *in vacuo* to afford ethyl 2-amino-4-methyl-4-pentenoate hydrochloride as an oil [3.11 g, 79.4%]: ^{1}H NMR [$CDCl_3$, 300 MHz] δ 1.25 - 1.32 [t, 3 H, J = 6.0 Hz], 1.81 [s, 3 H],

2.74 - 2.81 [m, 2 H], 4.22 - 4.29 [m, 2 H], 4.98 [d, 2 H, *J* = 12.0 Hz] ppm.

EXAMPLE 3

Preparation of (2*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide

To a stirred solution of *N*-Cbz-L-Leu-OH [5.6 g; 20.7 mmol] in anhydrous methylene chloride [CH_2Cl_2; 50 mL] at R.T. under Ar were added successively hydrobenzotriazole hydrate [HOBT; 5.6 g, 41.5 mmol], 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride [EDC; 4.0 g, 20.7 mmol], H-L-Leu-OCH_3 HCl [3.4 g, 18.8 mmol] and triethylamine [Et_3N; 2.9 mL, 20.7 mmol]. The reaction mixture was stirred for 16 h. The mixture was taken up in additional CH_2Cl_2 [30 mL], washed with sat. NaCl [2 x 10 mL], dried [$MgSO_4$], filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel [EA:H; 1:2] to afford the dipeptide *N*-Cbz-L-Leu-L-Leu-OCH_3 as a white solid [6.0 g, 64.1%]: ^1H NMR [$CDCl_3$, 300 Hz] δ 0.86 - 0.95 [ol-t, 12 H, *J* = 6.0 Hz], 1.48 - 1.74 [m, 6 H], 3.73 [s, 3 H], 4.20 - 4.25 [m, 1 H], 4.56 - 4.63 [m, 1 H], 5.11 [s, 2 H], 5.20 [d, 1 H, *J* = 6.0 Hz], 6.36 [d, 1 H, *J* = 6.0 Hz], 7.31 - 7.39 [m, 5 H] ppm.

To a stirred solution of *N*-Cbz-L-Leu-L-Leu-OCH_3 [6.0 g, 14.6 mmol] in MeOH/H_2O [3:1; 60 mL] at R. T. was added lithium hydroxide monohydrate [$LiOH{\cdot}H_2O$; 1.0 g, 43.9 mmol] and hydrogen peroxide [H_2O_2; 30% weight in H_2O; 4.5 mL, 43.9 mmol]. The reaction mixture was stirred for 3.5 h and then quenched with 10% HCl. The resulting mixture was extracted with EA [3 x 20 mL]. The combined organic extract was washed with sat. NaCl [2 x 10 mL], dried [$MgSO_4$] and concentrated *in vacuo* to afford *N*-Cbz-L-Leu-L-Leu-OH as a white solid [5.0 g, 90.5%]: ^1H NMR [$CDCl_3$, 300 MHz] δ 0.89 - 0.92 [t, 12 H, *J* = 3.0 Hz], 1.48 - 1.71 [m, 6 H], 4.11 - 4.13 [m, 1 H], 4.55 - 4.62 [m,

1 H], 5.09 [s, 2 H], 5.64 [d, 1 H, *J* = 9.0 Hz], 6.83 [d, 1 H, *J* = 9.0 Hz], 7.33- 7.40 [m, 5 H] ppm.

To a stirred solution of *N*-Cbz-L-Leu-L-Leu-OH [3.2 g, 8.5 mmol] in anhydrous CH_2Cl_2 [35 mL] at R.T. under Ar were added HOBT [2.3 g, 17.1 mmol], EDC [1.6 g, 8.5 mmol], ethyl 2-amino-4-methyl-4-pentenoate hydrochloride, as prepared in example 2, [1.5 g, 7.8 mmol] and Et_3N [1.2 mL, 8.5 mmol]. The reaction mixture was stirred for 16 h at R.T. The mixture was taken up in CH_2Cl_2 [30 mL]. The organic layer was washed with saturated aqueous sodium hydrogen carbonate [sat. $NaHCO_3$; 2 x 10 mL], 10% HCl [2 x 10 mL], sat. NaCl [2 x 10 mL], dried [$MgSO_4$], filtered and concentrated. The residue was purified by flash chromatography on silica gel [EA:H; 1:4] to afford (2*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[2-[ethyl(4-methyl-4-pentenoate)]amide as a white solid [1.9 g, 47.3%]: Reporting a mixture of diastereomers ^{1}H NMR [$CDCl_3$, 300 MHz] δ 0.88 - 0.92 [ol-m, 12 H], 1.21 - 1.29 [ol-m, 3 H], 1.51 - 1.71 [ol-m, 9 H], 2.39 - 2.52 [ol-m, 2 H], 4.13 - 4.21 [ol-m, 3 H], 4.47 - 4.82 [ol-m, 4 H], 5.10 [ol-m, 2 H], 5.32 [d, 1 H, *J* = 9.0 Hz], 6,44 - 6.77 [m, 2 H], 7.29 - 7.36 [ol-m, 5 H] ppm.

To a stirred solution of the above ethyl ester [1.9 g, 3.6 mmol] in anhydrous THF [10 mL] at 0° C under Ar was added lithium borohydride [$LiBH_4$; 0.16 g, 7.1 mmol]. Stirring was continued for 30 min at 0° C then the mixture was warmed to R. T. After 1 h, 1 N HCl [1 mL] was added to the reaction mixture, and then extracted with EA [3 x 20 mL]. The combined organic was washed with sat. NaCl [2 x 10 mL], dried [$MgSO_4$], filtered and concentrated *in vacuo* to afford the crude residue. The residue was purified by flash chromatography on silica gel [EA:H; 1:3] to yield the title compound as a white solid [1.4 g, 85.6%)]. Reporting a mixture of diastereomers ^{1}H NMR [$CDCl_3$, 300 MHz] δ 0.88 - 0.95 [ol-m, 12 H], 1.47 - 1.73 [ol-m, 9 H], 2.16 - 2.27 [ol-m, 2 H], 3.54 - 3.67 [ol-m, 2 H], 4.12 [ol-m, 2 H], 4.33 - 4.40 [ol-m, 1 H], 4.74 - 4.80

[ol-m, 2 H], 5.03 - 5.37 [ol-m, 3 H], 6.34 -6.37 [ol-m, 2 H], 7.30 - 7.40 [ol-m, 5 H] ppm.

EXAMPLE 4

Preparation of (1*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[2-(thiazole-hexanol)]amide

To a stirred solution of thiazole [0.11 mL, 1.55 mmol] in anhydrous ether [8 mL] at -78° C under Ar was slowly added 1.8 M *N*-butyl lithium in hexanes [*n*BuLi; 1.0 mL, 1.7 mmol]. After an additional 20 min of stirring at -78° C *N*-BOC-L-Nle *N*-methoxy-*N*-methylamide [0.17 g, 0.62 mmol] in anhydrous ether (5 mL) was added. Stirring was continued for 1 h at - 78° C then gradually warmed to R. T. The resulting mixture was treated with 1 N HCl [1 mL], 1 N NaOH [pH 9], and extracted with ether [3 x 10 mL]. The combined organic layers was washed with sat. $NaHCO_3$ [2 x 10 mL], sat. NaCl [2 x 10 mL], dried [$MgSO_4$], filtered and concentrated. Purification by flash chromatography on silica gel [EA:H; 1:5] afforded the (2*S*)-*N*-BOC-2-amino-thiazole-oxo-hexyl derivative as a white solid [0.14 g, 76%]: ^1H NMR [$CDCl_3$, 300 MHz] δ_ 0.86 [t, 3 H, *J* = 6.0 Hz], 1.23 - 1.62 [m, 13 H], 1.66 - 1.75 [m, 2 H], 5.32 - 5.46 [m, 2 H], 7.70 [d, 1 H, *J* = 3.0 Hz], 8.03 [d, 1 H, *J* = 6.0 Hz] ppm.

The above derivative [0.13 g, 0.44 mmol] was treated with 4 N HCl/dioxane [5 mL] at R. T. After 30 min the reaction mixture was concentrated *in vacuo*. The resulting solid was recrystallized [methanol (MeOH)/Ether] to give the hydrochloride as a white solid [0.1 gr, 75%]: ^1H NMR [CD_3OD, 300 MHz] δ 0.64 - 0.73 [t, 3 H, *J* = 6.0 Hz], 1.17 - 1.21 [m, 4 H], 1.76 - 1.99 [m, 2 H], 4.86 - 4.91 [m, 1 H], 7.72 - 7.98 [m, 2 H] ppm.

To the resulting hydrochloride [0.09 g, 0.33 mmol] in anhydrous CH_2Cl_2 [10 mL] at R. T. under Ar was added HOBT [0.1 g, 0.73 mmol], EDC [0.07 g, 0.36 mmol], *N*-Cbz-L-Leu-L-Leu-OH [0.09 g, 0.33 mmol] and Et_3N [0.09 mL, 0.66 mmol]. After 16 h CH_2Cl_2 [20 mL] was added,

and the organic layer was washed with sat. $NaHCO_3$ [2 x 10 mL], 1 N HCl [2 x 10 mL], sat. NaCl [2 x 10 mL], dried [$MgSO_4$], filtered and concentrated. Purification by flash chromatography on silica gel [EA:H;1:1] afforded (2*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[2-(thiazole-oxo-hexyl]amide as a white solid [0.16 gr, 88%]: ^{1}H NMR [$CDCl_3$, 300 MHz] δ 0.83 - 1.06 [m. 15 H], 1.20 - 2.15 [m, 12 H], 4.10 - 4.30 [m, 1 H], 4.48 - 4.61 [m, 1 H], 5.11 [s, 2 H], 5.15 - 5.25 [m, 1 H], 5.60 - 5.70 [m, 1 H], 6.32 - 6.50 [m, 1 H], 7.30 - 7.40 [m, 5 H], 7.70 [dd, 1 H, J = 6.0, 3.0 Hz], 8.05 [dd, 1 H, J = 6.0, 3.0 Hz] ppm.

To a stirred solution of the above ketone derivative [1.0 eq] in MeOH [50 mL] under Ar at 0 °C is added sodium borohydride [$NaBH_4$; 1.0 mmol]. Stirring is continued for 30 min at 0° C, then the mixture is warmed to R. T. After 1 h, 1 N HCl is added to the reaction mixture, and then extracted with EA. The combined organic extract is washed with 1 N HCl, sat. $NaHCO_3$, sat. NaCl, dried [$MgSO_4$], filtered and concentrated *in vacuo* to afford the crude residue. The residue is purified by flash chromatography on silica gel to yield the title compound.

EXAMPLE 5

Preparation of (2*SR*)-(3*SR*)-3-amino-1,1,1-trifluoro-2-heptanol

To a stirred solution of 1-nitropentane [1.0 g, 8.5 mmol] and tri-fluoroacetaldehyde ethyl hemiacetal [1.2 mL, 8.5 mL] was added potassium carbonate [K_2CO_3; 0.06 g, 0.43 mmol]. The reaction mixture was heated at 60° C under Ar for 3 h. The mixture was cooled to R.T., then taken up in EA (50 mL). The organic layer was washed with 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated to give (2*SR*)-(3*SR*)-3-nitro-1,1,1-trifluoro-2-heptanol as a crude oil (1.7 g, 93%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, 3 H, J = 7.2 Hz), 1.24 - 1.43 (m, 4 H), 2.04 - 2.11 (m, 2 H), 4.08 - 4.77 (m, 3 H) ppm.

To a stirred solution of the nitro-alcohol derivative (1.6 g, 7.4 mmol) in MeOH (10 mL) was added Raney Nickel (0.16 g, 10% by

weight). The mixture was placed under 35 psi of hydrogen gas (H_2) for 16 h, and then was filtered through celite. The celite was washed with MeOH (3 x 10 mL). The combined organic layers was concentrated to give (2*SR*)-(3*SR*)-3-amino-1,1,1-trifluoro-2-heptanol as an oil (0.8 g, 64.9%): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.89 - 0.95 (m, 3 H), 1.20 - 2.10 (m, 6 H), 3.30 - 4.40 (m, 4 H) ppm.

EXAMPLE 6

Preparation of (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide

To a stirred solution of (2*SR*)-(3*SR*)-3-amino-1,1,1-trifluoro-2-heptanol (0.36 g, 2.14 mmol) (as prepared in example 5) in anhydrous CH_2Cl_2 (20 mL) were added *N*-Ac-Leu-Leu-OH (0.67 g, 2.4 mmol), HOBT (0.33 g, 2.4 mmol), EDC (0.46 g, 2.4 mmol) and Et_3N (0.33 mL, 2.4 mmol). The reaction mixture was stirred for 18 h then washed with sat. $NaHCO_3$ (2 x 10 mL), 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (EA:H; 1:2) afforded the trifluoromethyl alcohol peptide derivative,the titile compound, as a white solid (0.85 g, 88.8%): Reporting a mixture of diastereomers ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 - 0.95 (ol-m, 15 H), 1.05 - 1.90 (ol-m, 12 H), 1.95 (s, 3 H), 3.91 - 4.50 (ol-m, 4 H) ppm.

EXAMPLE 7

Preparation of (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide

To a stirred solution of (2*SR*)-(3*SR*)-3-amino-1,1,1-trifluoro-2-heptanol (0.9 g, 3. 4 mmol) (prepared in example 5) in anhydrous CH_2Cl_2 (15 mL) at R.T. were added *N*-Cbz-L-Leu-OH (0.58 g, 3.1 mmol), HOBT (0.92 g, 6.8 mmol), EDC (0.65 g, 3.4 mmol) and Et_3N (0.47 mL, 3.4 mmol). The reaction mixture was stirred for 18 h then washed with sat. $NaHCO_3$ (2 x 10 mL), 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried

($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (EA:H; 1:4) afforded the trifluoromethyl alcohol peptide derivative,the titile compound, as a white solid (1.1 g, 82.6%): Reporting a mixture of diastereomers ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 - 0.95 (ol-m, 9 H), 1.29 - 1.65 (ol-m, 9 H), 4.00 - 4.17 (ol-m, 3 H), 4.59-5.46 (m, 4 H), 6.42-6.81 (m, 1 H), 7.29-7.38 (m, 5 H) ppm.

EXAMPLE 8

Preparation of *N*-valeroyl-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide

To a stirred solution of valeric acid (2 mL, 15.7 mmol) in anhydrous CH_2Cl_2 (40 mL) at R.T. were added HOBT (4.3 g, 31.5 mmol), EDC (3.0 g, 15.7 mmol), H-L-Leu-OCH_3.HCl (2.6 g, 14.3 mmol) and Et_3N (2.2 mL, 15.7 mmol). The reaction mixture was stirred for 18 h then taken up in additional CH_2Cl_2 (20 mL), washed with sat. $NaHCO_3$ (2 x 10 mL), 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (EA:H; 1:3) afforded *N*-valeroyl-L-Leu-OCH_3 as a colorless oil (2.7 g, 77.5%): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 - 1.03 (m, 12 H), 1.50 - 1.69 (m, 6 H), 2.20 - 2.25 (m, 2 H), 3.74 (s, 3 H), 4.62 - 4.70 (m, 1 H), 5.86 - 5.89 (d = 1 H, J = 9 Hz) ppm.

To a stirred solution of the above methyl ester in MeOH/H_2O (3:1) (30 mL) at R.T. was added LiOH·H_2O (0.80 g, 33.3 mmol). Reaction mixture was stirred for 1.5 h, quenched with 1 N HCl (15 mL) then extracted with EA (2 x 40 mL). The combined organic layers was washed with sat. NaCl (3 x 15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the acid as a white solid (2.4 g, 94.3%): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 - 0.97 (m, 12 H), 1.49 - 1.75 (m, 6 H), 2.23 - 2.25 (m, 2 H), 4.58 - 4.65 (m, 1 H), 5.98 (d, 1 H, J = 9 Hz) ppm.

To a stirred solution of the above acid (0.9 g, 3.9 mmol) in anhydrous CH_2Cl_2 (15 mL) were added successively HOBT (1.1 g, 7.8 mmol), EDC (0.76 g, 3.98 mmol) and (2*SR*)-(3*SR*)-3-amino-1,1,1-

trifluoro-2-heptanol (0.66 g, 3.6 mmol) (prepared as outlined in example 5). The reaction mixture was stirred for 18 h then washed with sat. $NaHCO_3$ (2 x 10 mL), 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (EA:H; 1:3) afforded the titile compound as a white solid (0.95 g, 67.2%): Reporting a mixture of diastereomers ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 - 0.95 (ol-m, 15 H), 1.31 - 1.83 (ol-m, 12 H), 2.17 - 2.23 (m, 2 H), 4.04 - 4.13 (ol-m, 2 H), 4.40 - 4.48 (m, 1 H), 6.04 -6.36 (m, 1 H), 6.95 -7.23 (m, 1 H) ppm.

EXAMPLE 9

Preparation of (*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[2-(phenylhexanol)]amide

To a stirred solution of *N*-BOC-L-Nle *N*-methoxy-*N*-methylamide (1.0 eq) in anhydrous THF at -78 °C under Ar is added slowly a solution of lithium 4-fluorobenzene (3 eq) generated *in situ*. The reaction mixture is gradually warmed to R.T. After 3 h, 1 N HCl is added to the reaction mixture, and then extracted with EA. The combined organic layers is washed with 1 N HCl, sat. $NaHCO_3$, sat. NaCl, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude residue. The residue is purified by flash chromatography on silica gel to give the ketone derivative.

The above intermediate (1.0 eq) is treated with 4 N HCl in dioxane at R.T. The reaction mixture is stirred for 1.5 h then concentrated *in vacuo*. The solid is treated with anhydrous ether and concentrated *in vacuo* to give 2*S*-amino-phenylhexanone hydrochloride.

To a stirred solution of 2*S*-amino-phenylhexanone hydrochloride (1.0 eq) in CH_2Cl_2 at R.T. is added successively *N*-Cbz-L-Leu-L-Leu-OH (1.2eq), HOBT (2.2 eq) and EDC (1.1 eq). The reaction mixture is stirred for 18 h then washed with sat. $NaHCO_3$, 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by

flash chromatography on silica gel affords the peptide ketone intermediate.

To a stirred solution of the above intermediate (1.0 eq) in MeOH at R.T. is added $NaBH_4$ (1.0 eq). The reaction mixture is stirred for 3 h, then taken up in EA washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel affords the title compound.

EXAMPLE 10

Preparation of of (2*SR*)-(3*S*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-butanol)]amide

To a stirred solution of *N*-BOC-L-Ala *N*-methoxy-*N*-methylamide (1.0 eq) in anhydrous THF at 0 °C under Ar is added lithium aluminum hydride ($LiAlH_4$) (1.0 eq). After 1 h the reaction mixture is treated with 1 N HCl then taken up in EA. The organic layer is washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered and concentrated. The resulting aldehyde is used in the next step without further purification.

To a stirred solution of the above aldehyde (1.0 eq) in anhydrous THF at 0 °C under Ar is added (trifluoromethyl)trimethylsilane (1.2 eq) in anhydrous THF followed by a catalytic amount of tetrabutylammonium fluoride (TBAF). The resulting siloxy compound is hydrolyzed with 1 N HCl. The reaction mixture is taken up in EA. The organic layer is washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel gives the *N*-BOC trifluoromethyl alcohol.

The above intermediate (1.0 eq) is treated with 4 N HCl in dioxane at R.T. The reaction mixture is stirred for 1.5 h then concentrated *in vacuo*. The solid is treated with anhydrous ether and concentrated *in vacuo* to give (2*SR*)-(3*S*)-3-amino-1,1,1-trifluoro-2-butanol hydrochloride.

To a stirred solution of (2*SR*)-(3*S*)-3-amino-1,1,1-trifluoro-2-butanol hydrochloride (1.0 eq) in CH_2Cl_2 at R.T. is added successively *N*-Cbz-L-Leu-L-Leu-OH (1.2eq), HOBT (2.2 eq) and EDC (1.1 eq). The reaction mixture is stirred for 18 h then washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel affords the title compound.

EXAMPLE 11

Preparation of (3*SR*)-(4S)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(ethyl 2,2-difluoro-3-hydroxy-octanoate)]amide

To a stirred solution of *N*-BOC-L-Nle *N*-methoxy-*N*-methylamide (1.0 eq) in anhydrous THF at 0 °C under Ar is added $LiAlH_4$ (1.0 eq). After 1 h the reaction mixture is treated with 1 N HCl then taken up in EA. The organic layer is washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered and concentrated. The resulting aldehyde is used in the next step without further purification.

To stirred solution of the freshly prepared above aldehyde (1.0 eq) and ethyl bromodifluoroacetate (3.0 eq) in anhydrous THF at R.T. under Ar is added Zn powder (4.0 eq). The reaction mixture is placed in a sonication bath at R.T. for 1 h. The reaction is poured onto ice/H_2O and the resulting slurry is filterd through celite, washing with ether. The aqueous layer is separated and extracted with EA. The combined organic layers is washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered and concentrated. The crude residue is purified by flash chromatography on silcal gel to give the α,α-difluoro-β-hydroxy-ethyl ester product.

The above intermediate (1.0 eq) is treated with 4 N HCl in dioxane at R.T. The reaction mixture is stirred for 1.5 h then concentrated *in vacuo*. The solid is treated with anhydrous ether and concentrated *in vacuo* to give the hydrochloride adduct.

To a stirred solution of the above hydrochloride product (1.0 eq) in CH_2Cl_2 at R.T. is added successively *N*-Cbz-L-Leu-L-Leu-OH (1.2eq), HOBT (2.2 eq) and EDC (1.1 eq). The reaction mixture is stirred for 18 h then washed with sat. $NaHCO_3$, 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel affords the title compound.

EXAMPLE 12

Preparation of *N*-BOC-(4*S*)-4-amino-1,1,1-trifluoro-2,2-difluoro-3-octanone

To a stirred solution of *N*-BOC-L-Nle *N*-methoxy-*N*-methylamide (1.0 eq) in anhydrous ether at -78 °C under Ar is added condensed pentafluoroethyl iodide (CF_3CF_2I) (4.0 eq). To this mixture is added methyllithium-lithium bromide (CH_3Li-LiBr) complex (4.0 eq) at a rate which maintains an internal reaction temperature below -65 °C. The reaction mixture is stirred for 2 h at -65 to -78 °C, then poured onto H_2O. The aqueous phase is acidified with 1 N HCl (pH = 3). The aqueous phase is extracted with ether. The combined organic layers is washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel affords the pentylfluoroethyl ketone, the title compound.

EXAMPLE 13

Preparation of (4*S*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-octanol)]amide

N-BOC-(4*S*)-4-amino-1,1,1-trifluoro-2,2-difluoro-3-octanone, prepared in example 12, is treated with 4 N HCl in dioxane at R.T. The reaction mixture is stirred for 1.5 h then concentrated *in vacuo*. The solid is treated with anhydrous ether and concentrated *in vacuo* to give the hydrochloride adduct.

To a stirred solution of the above hydrochloride product (1.0 eq) in CH_2Cl_2 at R.T. is added successively *N*-Cbz-L-Leu-L-Leu-OH (1.2eq), HOBT (2.2 eq) and EDC (1.1 eq). The reaction mixture is stirred for 18 h

then washed with sat. $NaHCO_3$, 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel affords the pentafluoroethyl ketone peptide.

To a stirred solution of the above ketone (1.0 eq) in MeOH at R.T. is added $NaBH_4$ (1.0 eq). The reaction mixture is stirred for 3 h, then taken up in EA washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel affords the title compound.

EXAMPLE 14

Preparation of (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-methyl-3-octanol)]amide

To a stirred solution of *N*-BOC-(4*S*)-4-amino-1,1,1-trifluoro-2,2-difluoro-3-octanone (1.0 eq), prepared in example 12, in anhydrous THF at -78 °C under Ar is added a 3.0 M solution of methylmagnesium chloride in THF (2.2 eq). The mixture is allowed to warm to R.T. After 1 h, the reaction mixture is treated with 1 N HCl and extracted with EA. The combined organic layers is washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel affords the desired tertiary alcohol.

The above tertiary alcohol (1.0 eq) is treated with 4 N HCl in dioxane at R.T. The reaction mixture is stirred for 1.5 h then concentrated *in vacuo*. The solid is treated with anhydrous ether and concentrated *in vacuo* to give the hydrochloride adduct.

To a stirred solution of the above hydrochloride product (1.0 eq) in CH_2Cl_2 at R.T. is added successively *N*-Cbz-L-Leu-L-Leu-OH (1.2eq), HOBT (2.2 eq) and EDC (1.1 eq). The reaction mixture is stirred for 18 h then washed with sat. $NaHCO_3$, 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel affords the the titile compound.

EXAMPLE 15

Preparation (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-methyl-2-heptanol)]amide

To a stirred solution of (2*SR*)-(3*SR*)-3-amino-1,1,1-trifluoro-2-heptanol (1.0 eq) (as prepared in example 5) in anhydrous CH_2Cl_2 (20 mL) at R.T. under Ar are added $(BOC)_2O$ (1.1 eq), DMAP (cat.) and Et_3N (2.0 eq). After 1 h, the reaction mixture is washed with sat. $NaHCO_3$, 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel affords the the *N*-BOC protected compound.

To a stirred solution of the above product (1.0 eq) in 1:1 CH_2Cl_2:THF at R.T. under Ar is added trifluoroacetic acid (TFA) (3.0 eq) and the Dess-Martin reagent (3.0 eq). The reaction mixture is stirred for 12 h and concentrated *in vacuo*. The resulting residue is treated with a mixture of EA, sat. $NaHCO_3$ and saturated aqueous sodium thiosulfate (sat. $Na_2S_2O_3$). The organic layer is separated and washed with sat. $NaHCO_3$, sat. $Na_2S_2O_3$, sat. NaCl, dried ($MgSO_4$), filtered and concentrated. The residue is purifed by flash chromatography on silica gel to give the desired trifluoromethyl ketone.

To a stirred solution of the above trifluoromethyl ketone (1.0 eq) in anhydrous THF at -78 °C under Ar is added a 3.0 M solution of methylmagnesium chloride in THF (2.2 eq). The mixture is allowed to warm to R.T. After 1 h, the reaction mixture is treated with 1 N HCl and extracted with EA. The combined organic layers is washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel affords the desired tertiary alcohol.

The above tertiary alcohol (1.0 eq) is treated with 4 N HCl in dioxane at R.T. The reaction mixture is stirred for 1.5 h then

concentrated *in vacuo*. The solid is treated with anhydrous ether and concentrated *in vacuo* to give the hydrochloride adduct.

To a stirred solution of the above hydrochloride product (1.0 eq) in CH_2Cl_2 at R.T. is added successively *N*-Cbz-L-Leu-L-Leu-OH (1.2eq), HOBT (2.2 eq) and EDC (1.1 eq). The reaction mixture is stirred for 18 h then washed with sat. $NaHCO_3$, 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel affords the the titile compound.

EXAMPLE 16

Preparation of (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1-(1'-phenyl-3'(trifluoromethyl)-pyrazoloxy)-2-heptanol)]amide

To the *N*-Cbz-L-Nle-CHN_2 (1.0 eq) is added HBr (g) and pyridine (5 mL). The mixture is taken up in EA and washed with 1 N HCl, sat. $NaHCO_3$, sat. NaCl, dried ($MgSO_4$), filtered and concentrated to give the bromomethyl ketone.

To a solution of the bromomethyl ketone (1.0 eq) in anhydrous dimethylformamide (DMF) under Ar at R.T. is added 5-hydroxy-1-phenyl-3-(trifluoromethyl)-pyrazole (2.0 eq) and potassium fluoride (2.0 eq). The reaction mixture is stirred at R.T. for 16 h, and extracted with EA. The combined organic layers is washed with sat. NaCl, sat. $NaHCO_3$, 1 N HCl, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel affords the furfurylthio-derivative. The derivative is treated with H_2/Pd(C) in MeOH to give the free amine.

To a solution of the above free amine (1.0 eq) in anhydrous CH_2Cl_2 at R.T. under Ar is added HOBT (2.0 eq), EDC (1.0 eq), Et_3N (1.0 eq) and *N*-Cbz-L-Leu-L-Leu-OH (1.1 eq). After 6 h the reaction mixture is washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$) filtered and concentrated. Purification by flash chromatography on silica gel gives the ketone.

To a stirred solution of the ketone in methanol at 0 °C is added $NaBH_4$ (1.0 eq). After 1 h the reaction mixture is warmed to R.T. The reaction mixture is stirred for 4 h, at R.T, then quenched by the addition of 1 N HCl (1 mL), concentrated, and extracted with EA. The combined organic layers is washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel gives the title alcohol.

EXAMPLE 17

Preparation of (2*SR*)-H-L-Leu *N*-[2-(ethyl 4-methyl-4-pentenoate)]amide hydrochloride

To a stirred solution of ethyl 2-amino-4-methyl-4-pentenoate hydrochloride (as prepared in example 2) (0.70 g, 3.6 mmol) in CH_2Cl_2 (10 mL) at R. T. under Ar were added *N*-BOC-L-Leu-OH (1.0 g, 4.0 mmol), HOBT (1.19 g, 7.9 mmol), EDC (0.76 g, 4.0 mmol) and Et_3N (0.55 mL, 4.0 mmol). The reaction mixture was taken up in additional CH_2Cl_2 (20 mL) and washed with sat. $NaHCO_3$ (2 x 10 mL), 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel (EA:H; 1:1) to afford the dipeptide ethyl ester as a white solid (1.05 g, 78.6%): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 - 0.97 (m, 6 H), 1.25 - 1.30 (t, 3 H, J = 6 Hz), 1.44 - 1.74 (m, 15 H), 2.37 - 2.57 (m, 2 H), 4.15 - 4.22 (m, 2 H), 4.64 - 4.94 (m, 4 H) ppm.

To the above ester (1.0 g, 2.7 mmol) was added 4 N HCl/dioxane (15 mL), stirred at R.T. for 4 h, then the solvent was removed. Co-evaporation with ether (3 x 5 mL) yielded the title compound as a white solid (0.8 g, 96.3%): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 - 1.00 (m, 6 H), 1.21 - 1.31 (m, 3 H), 1.44 - 1.84 (m, 6 H), 2.34 (m, 2 H), 4.16 - 4.75 (m, 4 H) ppm.

EXAMPLE 18

Preparation of (2*SR*)-*N*-[(2*S*)-2-benzoxy-4-methylpentanoyl]-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide

To a stirred solution of L-Leu-OH (5.0 g, 38.2 mmol) in 1 N H_2SO_4 (50 mL) at 0° C was slowly added over 1 1/2 h a solution of sodium nitrite ($NaNO_2$) (7.5 g, 0.11 mmol) in water (20 mL) while maintaining the temperature at 0° C. The reaction mixture was gradually warmed to R.T., stirred for 24 h, and concentrated to give a white solid. The solid was extracted with ether (5 x 50 mL). The combined organic layers was dried ($MgSO_4$), filtered and concentrated to give (2*S*)-2-hydroxy-4-methylpentanoic acid as an oil (4.1 g, 81.2%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (d, 6 H, J = 12.0 Hz), 1.57 - 1.67 (m, 2 H), 1.82 - 1.93 (m, 1 H), 4.36 (t, 1 H, J = 6.0 Hz) ppm.

To a stirred solution of the acid (4.0 g, 30.5 mmol) in anhydrous DMF (20 mL) at R. T. under Ar was added cesium carbonate (Cs_2CO_3) (12.9 g, 40.0 mmol) and methyl iodide (5.7 g, 40.0 mmol). The reaction mixture was stirred for 16 h then taken up in EA (100 mL). The organic layer was washed with sat. $NaHCO_3$ (3 x 20 mL), 1 N HCl (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (EA:H; 1:4) gave methyl (2*S*)-2-hydroxy-4-methylpentanoate as a colorless oil (2.5 g, 57%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 - 1.01 (m, 6 H), 1.56 - 1.74 (m, 2 H), 1.87 - 1.96 (m, 1 H), 3.79 (s, 3 H), 4.24 (q, 1 H, J = 6.0 Hz) ppm.

To a stirred solution of methyl (2*S*)-2-hydroxy-4-methylpentanoate (0.5 g, 3.4 mmol) in anhydrous CH_2Cl_2 (10 mL) at R.T. under Ar was added benzyl 2,2,2-trichloroacetimidate (1.4 mL, 6.8 mmol) and trifluoromethylsulfonic acid (25 μl). After 30 min the reaction mixture was taken up in CH_2Cl_2 (20 mL). The organic layer was washed with sat. NaCl (2 x 10 mL), 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography

on silica gel (EA:H; 1:10) afforded methyl (2*S*)-2-benzoxy-4-methylpentanoate as an oil (0.6 g, 73.5%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 - 0.98 (m, 6 H), 1.40 - 1.58 (m, 1 H), 1.69 - 1.87 (m, 2 H), 3.74 (s, 3 H), 3.93 - 4.06 (m, 1 H), 4.42 (d, 1 H, J = 12.0 Hz), 4.68 - 4.80 (m, 1 H), 7.14 - 7.32 (m, 5 H) ppm.

To the above methyl (2*S*)-2-benzoxy-4-methylpentanoate (0.69 g, 2.92 mmol) in MeOH/H_2O (5 mL/1 mL) was added $LiOH{\cdot}H_2O$ (0.28 g, 11.7 mmol) and 30% H_2O_2 (0.3 mL, 11.7 mmol). After stirring the reaction mixture for 24 h, the mixture was treated with 1 N HCl (pH = 3) and the methanol was removed *in vacuo*. The aqueous layer was extracted with EA (4 x 15 mL). The combined organic layers was washed with 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. (2*S*)-2-benzoxy-4-methylpentanoic acid was isolated as a colorless oil (0.65 g, 100%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 - 1.60 (m, 6 H), 1.53 - 1.62 (m, 1 H), 1.73 - 1.90 (m, 2 H), 3.99 - 4.50 (m, 1 H), 4.46 (d, 1 H, J = 12.0 Hz), 4.72 (d, 1 H, J = 12.0 Hz) 7.10 - 7.26 (m, 5 H) ppm.

To a solution of the product from example 17 (0.5 g, 1.63 mmol) in anhydrous CH_2Cl_2 (10 mL) at R.T. under Ar was added the above acid (0.4 g, 1.8 mL), HOBT (0.24 g, 1.8 mmol), EDC (0.35 g, 1.8 mmol) and Et_3N (0.25 mL, 1.8 mmol). After 16 h the reaction mixture was washed with sat. $NaHCO_3$ (2 x 10 mL), 1 N HCl (2 x 10 ml), sat. NaCl (2 x 10 mL) dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography afforded the ethyl ester (0.5 g, 62.5%): Reporting a mixture of diastereomers ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76 (t, 3 H, J = 6.0 Hz), 0.91 - 0.99 (ol-m, 12 H), 1.22 - 1.9 (ol-m, 9 H), 2.05 - 2.18 (ol-m, 1 H), 2.34 - 2.43 (ol-m, 1 H), 3.71 - 4.95 (ol-m, 9 H), 7.20 - 7.38 (ol-m, 5 H) ppm.

To a solution of the ester (0.5 g, 1.0 mmol) in anhydrous THF (10 mL) at R.T. under Ar was added $LiBH_4$ (0.02g, 1.0 mmol). Reaction mix-

ture was stirred for 4 h then quenched by the addition of 1 N HCl (1 mL), concentrated, and extracted with EA (3 x 10 mL). The combined organic layers was washed with sat. $NaHCO_3$ (2 x 10 mL), 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (EA:H; 1:3) gave the title alcohol as an oil (0.13 g, 30%): Reporting a mixture of diastereomers ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.72 - 0.98 (ol-m, 2 H), 1.10 - 2.21 (ol-m, 11 H), 3.58 - 4.92 (ol-m, 9H), 7.0 - 7.50 (ol-m, 7 H) ppm.

EXAMPLE 19

Preparation of (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-Leu *N*-[3-(2-hydroxy-heptanoic acid)]amide

To a stirred solution of *N*-BOC-L-Nle *N*-methoxy-*N*-methylamide (1.0 eq) in anhydrous THF (10 mL) at 0° C under Ar is added $LiAlH_4$ (1.0 eq), and stirred for 3 h at 0° C followed by the addition of 1 N HCl (1 mL). The mixture is taken up in EA then washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered and concentrated to afford the *N*-BOC-L-norleucinal as a crude residue. To the residue is added an ice-cold solution of $NaHSO_3$ (8 eq) and the mixture is stirred for 24 h at 5° C. To the resulting suspension is added EA and an aqueous potassium cyanide solution (KCN) (8 eq). The reaction mixture is stirred at R.T. for 4 h. The organic phase is washed with water and concentrated to give the cyanohydrin.

The cyanohydrin is hydrolyzed in 4 N HCl/dioxane under reflux for 12 h. The solvent is removed and the residue is washed with anhydrous ether to give the hydrolyzate. To a stirred solution of *N*-Cbz-L-Leu-Leu-OH (1.0 eq) in anhydrous CH_2Cl_2 under Ar at R.T. is added CDI (1.1 eq). After 30 min of stirring Et_3N (2 eq) and the hydrolyzate (1.0 eq) are added. The mixture is stirred for 6 h, then concentrated. The residue is triturated with 1 N HCl washed with water and dried *in vacuo* to afford the title compound.

EXAMPLE 20

Preparation of (2*SR*)- (3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(methyl 2-hydroxy-heptanoate)]amide

To the product obtained from example 19 in anhydrous ether at 0° C is added diazomethane. After 3 h the solvent is removed and the residue is purified by flash chromatography on silica gel to give the desired product.

EXAMPLE 21

Preparation of (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(benzyl 2-hydroxy-heptamide)]amide

To the product of example 19 in anhydrous CH_2Cl_2 under Ar at R.T. is added HOBT (1.0 eq), EDC (1.0 eq), Et_3N (1.0 eq) and benzylamine (1.0 eq). After 6 h the reaction mixture is washed with sat. $NaHCO_3$, sat. 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered and concentrated. The residue is purified by flash chromatography on silica gel to afford the desired product.

EXAMPLE 22

Preparation of (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(benzyl 3-hydroxy-octamide)]amide

To a solution of *N*-BOC-L-norleucinal (1.0 eq), prepared by reducing *N*-BOC-L-Nle *N*-methoxy-*N*-methylamide as described in example 19, in THF at -78° C under Ar is added ethyl lithioacetate (2.2 eq) prepared *in situ* by the addition of *n*BuLi (2.2 eq) to excess anhydrous ethyl acetate. After 3 h, the reaction mixture is treated with 1 N HCl, and the organic layer is washed with 1 N HCl, sat. $NaHCO_3$, sat. NaCl, dried (Mg SO_4), filtered and concentrated. Purification by flash chromatography on silica gel gives the ester.

The ester is treated with 4 N HCl/dioxane for 30 min and concentrated *in vacuo*. The resulting solid is taken up in anhydrous ether and concentrated *in vacuo* to give the hydrochloride. The hydrochloride is used without further purification in the next step.

To the hydrochloride (1.0 eq) in anhydrous CH_2Cl_2 at R.T. under Ar is added HOBT (2.0 eq), EDC (1.0 eq), Et_3N (1.0 eq) and *N*-Cbz-L-Leu-Leu-OH (1.1 eq). After 6 h, the organic is washed with sat. $NaHCO_3$, 1 N HCl, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel gives the ester.

To a stirred solution of the above ester (1.0 eq) in $MeOH/H_2O$ is added $LiOH{\cdot}H_2O$ (2 eq) and H_2O_2 (1.0 eq). After 4 h the reaction is quenched by the addition of 1 N HCl and then extracted with EA (2x). The combined organic layers is washed with sat. NaCl, dried ($MgSO_4$) and concentrated to give the acid.

To a solution of the acid (1.0 eq) in anhydrous CH_2Cl_2 at R.T. under Ar is added EDC (1.0 eq), HOBT (1.0 eq), Et_3N (1.0 eq) and benzylamine (1.1 eq). The reaction mixture is stirred for 3 h, washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$), filtered, concentrated and purified by flash chromatography on silica gel affording the title compound.

EXAMPLE 23

Preparation of (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu N-[3-(1-furfylthio-2-heptanol)]amide

To *N*-Cbz-L-Nle-CHN_2 (1.0 eq) is added HCl and pyridine (5 mL). The mixture is taken up in EA and washed with 1 N HCl, sat. $NaHCO_3$, sat. NaCl, dried ($MgSO_4$), filtered and concentrated to give the chloromethyl ketone.

To a solution of the chloromethyl ketone (1.0 eq) in anhydrous THF under Ar at R.T. is added furfuryl mercaptan (2.0 eq) and Et_3N (2.0 eq). The reaction mixture is stirred at R.T. for 16 h, and extracted with EA. The combined organic layers is washed with sat. NaCl, sat. $NaHCO_3$, 1 N HCl, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel affords the furfurylthio-derivative. The derivative is treated with $H_2/Pd(C)$ in MeOH to give the free amine.

To a solution of the above amine (1.0 eq) in anhydrous CH_2Cl_2 at R.T. under Ar is added HOBT (2.0 eq), EDC (1.0 eq), Et_3N (1.0 eq) and *N*-Cbz-L-Leu-L-Leu-OH (1.1 eq). After 6 h the reaction mixture is washed with sat. $NaHCO_3$, 1 N HCl, sat. NaCl, dried ($MgSO_4$) filtered and concentrated. Purification by flash chromatography on silica gel gives the ketone.

To a stirred solution of the ketone in methanol at 0 °C is added $NaBH_4$ (1.0 eq). After 1 h the reaction mixture is warmed to R.T. The reaction mixture is stirred for 4 h, at R.T, then quenched by the addition of 1 N HCl (1 mL), concentrated, and extracted with EA (3 x 10 mL). The combined organic layers is washed with sat. $NaHCO_3$ (2 x 10 mL), 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (EA:H; 1:3) gave the title alcohol.

EXAMPLE 24

Preparation of (2*SR*)-*N*-[(2*R*)-[2-(1'-phenyl-1'-propene)-4-methylpentanoyl]]-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide

To a stirred solution of 4-methylvaleric acid (10.8 mL, 86.1 mmol) in anhydrous CH_2Cl_2 (25 mL) was added thionyl chloride (25 mL, 0.34 mmol). The mixture was placed under reflux for 24 h. Then solvent and excess thionyl chloride were removed *in vacuo* to give the acid chloride as an oil (10.2 g,90%). The acid chloride was used directly in the next step.

To the acid chloride (2.7 g, 20.3 mmol) in anhydrous CH_2Cl_2 (50 mL) at R.T. under Ar was added DMAP (0.10 g), Et_3N (4.6 mL, 33.8 mmol) and (4*S*, 5*R*)-(-)-4-methyl-5-phenyl-2-oxazolidinone (3.0 g, 16.9 mmol). The reaction mixture was stirred for 16 h then washed with 1 N HCl (2 x 10 mL), sat. $NaHCO_3$ (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (EA:H; 1:20) afforded the imide as an oil (2.8 g, 61%): ^1H

NMR ($CDCl_3$, 300 MHz) δ 0.80-1.10 (m, 9 H), 1.60-1.90 (m, 3 H), 2.40-2.55 (m, 2 H), 4.80-4.90 (m, 1 H), 5.70-5.80 (m, 1 H), 7.20-7.50 (m, 5 H) ppm.

To a solution of the imide (2.5 g, 9.14 mmol) in anhydrous THF (40 mL) at -78° C under Ar was slowly added a 1.5 M solution of lithium diisopropylamide (LDA) in anhydrous THF (6.0 mL, 9.14 mmol) followed by cinnamyl bromide (1.8 g, 9.14 mL) in anhydrous THF (10 mL). The reaction mixture was stirred at -78° C for 1 h then gradually warmed to R.T. Stirring was continued at R.T. for 1 h then the mixture was treated with 1 N HCl (5 mL). The solvent was removed and the aqueous was taken up in EA (70 mL). The aqueous was separated and the organic was washed with sat. NaCl (2 x 10 mL), 1 N HCl (2 x 10 mL), sat. $NaHCO_3$ (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$) filtered and concentrated. Purification by flash chromatography on silica gel (EA:H; 1:4) afforded the alkylated derivative as an oil (3.5 g, 98.7%): ^1H NMR ($CDCl_3$, 300 Mhz) δ 0.73 (d, 3 H, J = 6.0 Hz), 0.80-0.92 (m, 6 H), 1.14-1.40 (m, 1 H), 1.48-1.79 (m, 1 H), 1.75-1.84 (m, 1 H), 2.42 (m, 2 H), 4.10-4.20 (m, 1 H), 4.71-4.78 (m, 1 H), 5.28 (d, 1 H, J = 9.0 Hz), 6.35 (m, 1 H), 6.45 (m, 1 H), 7.21-7.25 (m, 5 H) ppm.

To a solution of the above product (0.65 g, 1.66 mmol) in 3:1 $MeOH/H_2O$ (20 mL) at R.T. was added $LiOH{\cdot}H_2O$ (0.61 g, 4.98 mmol) and 30% H_2O_2 (0.83 mL). The reaction mixture was stirred for 4 h. The mixture was cooled to 0° C and quenched by the addition of 1 M $Na_2S_2O_3$ (1.6 mL) and allowed to warm to R.T. After 14 h the resulting solution was poured onto sat. $NaHCO_3$ (20 mL). The aqueous was extracted with CH_2Cl_2 (3 x 30 mL) then acidified with 1 N HCl (pH = 3). The aqueous was then extracted with CH_2Cl_2 (3 x 20 mL) and the combined organics is dried (MgSO4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (EA:H; 1:1) to give (2*S*)-2-(1'-phenyl-1'-propene)-4-methylpentanoic acid as an oil (0.30 g, 78.0%): ^1H NMR

($CDCl_3$, 300 MHz) δ 0.88-1.01 (m, 6 H), 1.29-1.42 (m, 3 H), 1.59-1.70 (m, 2 H), 2.55 (m, 3 H), 6.13 (m, 1 H), 6.47 (d, 1 H, J = 6.0 Hz), 7.31-7.40 (m, 5 H) ppm.

To a stirred solution of L-Leu-OMe HCl (0.14 g, 0.70 mmol) and (2S)-2-(1'-phenyl-1'-propene)-4-methylpentanoic acid (0.16 g, 0.69 mmol) in anhydrous CH_2Cl_2 (15 mL) at R.T. were added HOBT (0.19 g, 1.38 mmol), EDC (0.15 g, 0.78 mmol) and Et_3N (0.91 mL, 0.70 mmol). After 16 h the reaction mixture was washed with sat. $NaHCO_3$ (2 x 10 mL), 1 N HCl (x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification of the crude residue by flash chromatography on silica gel (EA:H; 1:1) afforded the methyl ester as an oil (0.24 g, 95%): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.76 - 0.78 (d, 3 H, J = 6.0 Hz), 0.82 - 1.06 (m, 3 H), 1.26 - 1.41 (m, 1 H), 1.44 - 1.72 (m, 2 H), 2.22 - 2.30 (m, 2 H), 2.35 - 2.46 (m, 1 H) 3.72 (s, 3 H), 4.57 (m, 1 H), 6.16 (m, 1 H), 6.43 (m, 1 H), 7.25 - 7.41 (m, 5 H) ppm.

To the above methyl ester (0.28 g, 0.78 mmol) in MeOH/H_2O (15 mL-5 mL) with stirring at 0° C was added 1 N LiOH·H_2O (0.95 mL) and 30% H_2O_2 (1.4 mL). After 2 h 1 N HCl (4 mL) was added and the aqueous layer was extracted with EA (3 x 30 mL). The combined organics was washed with sat. NaCl (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated to give a crude residue. Purification by flash chromatography on silica gel (EA:H; 1:1) afforded the acid as an oil (0.21g, 0.61 mmol): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.59 - 1.10 (m, 12 H), 1.12 - 1.71 (m, 6 H), 2.60 - 2.63 (m, 3 H), 4.45 (m, 1 H), 6.21 (m, 1 H) 6.40 (m, 1 H), 7.25 - 7.41 (m, 5 H) ppm.

To a stirred solution of the acid (0.25 g, 0.72 mmol) and ethyl 2-amino-4-methyl-4-pentenoate (0.16 g, 0.8 mmol) in anhydrous CH_2Cl_2 (15 mL) at R.T. were added HOBT (0.19 g, 1.44 mmol), EDC (0.15 g, 0.79 mmol) and Et_3 N (0.12 mL, 0.80 mmol). After 4 h the reaction mixture was washed with sat. $NaHCO_3$ (2 x 10 mL), 1 N HCl (2 x 10

mL), sat. NaCl (2 x 10mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel (EA:H; 1:1) to give (*2SR*)-[(*2R*)-[2-(1'-phenyl-1'-propene)-4-methyl pentanoyl]]-L-Leu *N*-[2-(ethyl 4-metyl-4-pentenoate)]amide as a solid (0.18g, 51%): ^1H NMR $CDCl_3$, 300 MHz) δ 0.81 - 1.10 (m, 12 H), 1.30 - 1.73 (m, 15 H), 2.27 - 2.51 (m, 2 H), 4.14 - 4.17 (m, 2 H), 4.22 - 4.49 (m, 2 H), 4.59 (m, 1 H), 6.21 (m, 1 H), 6.43 (m, 1 H), 7.17 - 7.19 9m, 2 H), 7.25 - 7.41 (m, 5H) ppm.

To the above ethyl ester (0.3 g, 0.62 mmol) in anhydrous THF (20 mL) at 0° C under Ar with stirring was added $LiBH_4$ (47 mg, 2.15 mmol). After 30 min at 0° C the reaction mixture was warmed to R.T. Stirring was continued for 2 h then quenched with 1 N HCl (2mL). The mixture was extracted with EA (3 x 10 mL). The combined organic layers was washed with sat. $NaHCO_3$ (2 x 10 mL), 1 N HCl (2 x 10 mL), sat. NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification of the crude by flash chromatography on silica gel (EA) yielded the alcohol as an oil (0.24 g, 87%): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.72 - 1.02 (m, 12 H), 1.20 - 1.86 (m, 13 H), 2.21 - 2.56 (m, 4 H), 3.60 - 3.68 (m, 2 H), 4.21 - 4.25 (m, 1 H), 4.80 - 4.85 (m 1 H), 6.10 - 6.15 (m, 1 H), 6.45 - 6.50 (m, 1 H), 7.17 - 7.19 (m, 2 H), 7.25 - 7.35 (m, 5 H) ppm.

EXAMPLE 25

Preparation of (*2SR*)-*N*-Ac-L-Leu-L-Leu *N* [2-(trans-4-hexanol)]amide

The title compound was isolated as a white solid (1.4 g, 80.3%) following the procedure outlined in example 3: Reporting a mixture of diastereomers ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 - 0.97 (ol-m, 12 H), 1.53 - 1.80 (ol-m, 9 H), 2.00 - 2.32 (ol-m, 5 H), 3.49 - 3.90 (ol-m, 3 H), 4.31 - 4.71 (ol-m, 2 H), 5.33 - 5.56 (ol-m, 2 H), 6.95 - 8.10 (ol-m, 3 H) ppm.

EXAMPLE 26

Preparation of (*2SR*)-*N*-Ac-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide

The title compound was isolated as a white solid (0.9 g, 62.0%) following substantially the same procedure described in example 3: Reporting a mixture of diastereomers ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 - 0.91 (ol-m, 12 H), 1.58 - 1.72 (ol-m, 9 H), 1.98 - 2.02 (d, 3 H), 4.26 - 4.42 (ol-m, 3 H), 4.62 - 4.80 (ol-m, 2 H), 6.00 -6.05 (m, 1 H), 6.70 - 6.82 (ol-m, 2 H), 9.53 - 9.55 (d, 1 H) ppm.

EXAMPLE 27

Preparation of *N*-Dansyl-L-Leu-L-Leu-DL-norleucinol

The title compound was isolated as a pale yellow solid (0.13 g) using the methodology described in Example 3.

EXAMPLE 28

Preparation of *N*-Ac-L-Phe-L-Leu-DL-norleucinol

The title compound *N*-Ac-L-Phe-L-Leu-DL-norleucinol was obtained as a white solid (0.19 g) following substantially the same procedure described in Example 3.

EXAMPLE 29

ASSAYS FOR IDENTIFICATION OF COMPOUNDS HAVING ACTIVITY AS MODULATORS OF THE PROCESSING OF APP

A. Immunoblot assay for Aβ peptide

Human glioblastoma cells (ATCC Accession No. HTB16) were stably transfected with a DNA expression vector encoding a 695 amino acid isoform variant of the amyloid precursor protein (APP) containing the familial Swedish double mutations at codons 670 and 671 (K to N and M to L, respectively; see Mullan et al. (1992) Nature Genet. 1:345-347) and an additional mutation at codon 717 (V to F; see Murrell et al. (1991) Science 254:97-99) to produce cells designated HGB 717/Swed. High levels of Aβ are detectable in the conditioned medium isolated from HGB 717/Swed cultured cells. The medium also contains larger secreted

fragments, α-sAPP$_{695}$, which are alternatively processed APP fragments whose generation precludes Aβ formation.

HGB 717/Swed cells were grown at 37°C under a 5% carbon dioxide atmosphere in Dulbecco's modified eagle medium (DMEM; Gibco) supplemented with 10% heat-inactivated fetal calf serum, 0.45% glucose, 2 mM L-glutamine, 100 units/ml penicillin, and 100 μg/ml streptomycin sulfate (Gemini Bioproducts). Approximately 1 X 10^6 cells were incubated overnight in 5 ml of DMEM containing varying μM final concentrations of desired test compounds or a DMSO control. Conditioned medium was collected, and unwanted cells and debris were removed by sedimentation at 3,000 rpm at 4°C.

Aβ peptides were isolated from the medium by immunoaffinity purification using an Aβ-specific antibody. To reduce the interaction of non-specific binding of unrelated proteins, such as serum proteins, to the Aβ antibody, the medium was pre-treated with rabbit antisera and Protein A Sepharose (Pharmacia) for 4 hours at 4°C. The sepharose-bound material was removed by centrifugation at 3,000 rpm at 4°C for 10 min, and Aβ peptides were immunoaffinity purified from the clarified medium by incubation overnight with an affinity purified polyclonal rabbit antibody (referred to as 2939) prepared against a synthetic Aβ peptide corresponding to amino acids 1 to 28. Protein A-conjugated sepharose was added to immobilize the Aβ-antibody complexes, and the resin was pelleted by centrifugation at 3,000 rpm at 4°C for 10 min. The Aβ-antibody complexes were eluted from the matrix by denaturing the complex by boiling in the presence of SDS.

Equal portions of each sample were loaded on 16% Tricine gels (Novex), and subjected to electrophoresis. Resolved proteins were transferred from the gel to Hybond nitrocellulose (Amersham, Arlington Heights, IL) by electroblotting, and incubated with the commercially available monoclonal antibody 6E10 (obtained from Drs. Kim and

Wisniewski, Institute for Basic Research, NY, see, published International PCT application WO 90/12871), which specifically recognizes Aβ residues 1 to 17. Specifically bound antibody was detected using a biotinylated goat anti-mouse IgG secondary antibody (Sigma), followed by the addition of streptavidin conjugated to horseradish peroxidase (Amersham, Arlington Heights, IL), and visualized by luminescent detection (Amersham). Levels of Aβ peptides were determined by laser densitometry of visualized films. A positive result in the assay is a decrease in the formation of the 4-kDa Aβ peptides in cells treated with test compounds relative to the DMSO control. Selected compounds provided herein were tested for and exhibited activity in this assay.

B. ELISA assay for total sAPP

Human glioblastoma cells (ATCC Acession No. HTB16) were stably transfected with a DNA expression vector encoding the 695 amino acid isoform of the amyloid precursor protein (APP_{695}). The resulting cells are designated HGB695 cells. High levels of secreted proteolytic processed fragments of APP_{695} ($sAPP_{695}$) are detectable in the culture medium.

Approximately 1 X 10^5 cells were plated into 12-well dishes and were grown for 72 hours at 37°C under a 5% carbon dioxide atmosphere in 1 ml of Dulbecco modified eagle medium (DMEM) supplemented with 10% heat-inactivated fetal calf serum, 0.45% glucose, and 100 units/ml penicillin, 100 μg/ml streptomycin sulfate and 2 mM L-glutamine. Following incubation, the medium was removed and 1 ml of supplemented DMEM medium containing 5 μl of DMSO or DMSO containing the desired test compound within a range between about 5 and about 100 μM (final concentration in the well), was added to each well, and incubation was continued for 24 hours. Unwanted cells and debris were removed by sedimentation at 3,000 x g for 10 min at room temperature. Supernatants were stored at -20°C for analysis.

In order to determine the amount of sAPP in the supernatants, a capture antibody that recognizes an epitope located in the amino terminus of APP, such as P2-1 (see, e.g., U.S. Patent No. 5, 270,165) or a goat affinity-purified IgG antibody raised against wildtype $sAPP_{695}$, was attached to the wells of a 96-well microtiter plate by incubating the antibody in the plate for 60 min at 37°C. The plates were washed three times with 0.3 ml of 0.1% Tween-20 in phosphate-buffered saline (PBS). The non-specific interaction of unrelated proteins (such as serum proteins that may interfere with the analysis) with the antibody was reduced by incubating the pre-treated wells for 30 min at 37 ° C with a solution of 0.5% casein or 0.5% gelatin in PBS (150-200 μl/well). Wells were washed thoroughly with 0.1% Tween-20 in PBS prior to analysis of samples.

The conditioned medium supernatant was diluted 1:20 in 0.95 ml of 0.1% CHAPS (3-[(3-cholamidopropyl)-dimethylammonio]-1-propane-sulfonate) in PBS. Supernatant samples (50 or 100 μl/well) or sAPP standards (50 or 100 μl/well) of a range about 5 to 50 ng/ml were added to the pre-treated wells and incubated for 1-2 hr at 37°C. The supernatant was removed and each sample well was washed as described above. A horseradish peroxidase (HRP) conjugated goat affinity purified antibody, raised against $sAPP_{695}$, was diluted in 0.1% Tween-20 in PBS and 10% goat serum and employed as the "signal antibody". The unbound antibody was removed by washing, and to each well, 0.1 ml of the chromagenic substrate K-Blue Solution (Elisa Technologies, Lexington, KY) was added and samples were incubated in the absence of visual light for 15 min at ambient temperature. Reactions were stopped by the addition of 0.1 ml of a 9.8% solution of phosphoric acid. The optical density of samples was measured by spectrophotometry at 450 nm. The concentration of $sAPP_{695}$ peptides in the conditioned medium was estimated from the $sAPP_{695}$ standard curve. Samples were analyzed in

duplicate with the appropriate standards and reference controls [i.e., a known protease inhibitor compound, such as *N*-acetylleucylleucylnorleucinal of given potency and concentration].

C. Cell lysate assay

In this assay, the effect of compounds on the modulation of the generation of partially processed C-terminal Aβ-containing amyloidogenic peptides is examined. HGB695 human glioblastoma cells were employed and grown in 12-well dishes essentially as described in Example 29B with the following modifications. The DMEM growth media were supplemented with varying μM concentrations of compounds or DMSO control and 100 μM leupeptin and 1 μM PMA phorbol ester and were incubated with cell cultures for 16 hours and cells were grown to approximately 2.5 X 10^6 cells per well.

Harvested cells from each well were lysed in 100 μl of lysis buffer containing 50 mM Tris-HCl, pH 7.8, 150 mM NaCl, 1% NP-40, 0.1% SDS and 0.5% deoxycholate supplemented with 1 mM PMSF. Equal volumes of cell lysates in Laemmli SDS buffer were loaded onto 16% SDS-Tricine polyacrylamide gels (Novex) and subjected to electrophoresis. Separated proteins were transferred to supported nitrocellulose (BioRad) by electroblotting. Nonspecific binding of proteins to the nitrocellulose membrane was blocked by incubating in a solution of 5% non-fat dried milk in PBS. The nitrocellulose membrane was washed three times in PBS and then incubated in PBS containing a 1:5000 dilution of a rabbit polyclonal antibody raised against the C-terminal 19 amino acids of APP (provided by S. Gandy, Rockefeller University, NY). The nitrocellulose membrane was washed as described above and incubated with a secondary biotinylated goat anti-rabbit IgG antibody. Specifically bound antibody was detected using a streptavidin horseradish peroxidase conjugate, and visualized in combination with an enhanced chemoluminescent detection kit (Amersham). Potentially amyloidogenic

peptides greater than 9 and less than 22 kDa were quantitated by densitometric scans of developed films within the linear range as described in Example 29B. A positive result for a compound in the cell lysate assay is denoted by a decrease in the levels of the protein bands greater than 9 and less than 22 kDa relative to the appropriate control samples.

D. ELISA assay for α-sAPP

Human HGB695 glioblastoma cells transfected with DNA encoding the 695 amino acid isoform of APP were grown and treated with test compound or DMSO as described in Example 29B. Media from the cultured cells were obtained as described in Example 29B and analyzed for α-sAPP in an ELISA assay as follows. The wells of a 96-well microtiter plate were coated with a monoclonal antibody that specifically recognizes the amino terminus of human APP (e.g., monoclonal antibody P2-1) or with a rabbit polyclonal antibody (designated 3369) generated against a peptide including Aβ amino acid residues 1-15 by incubating the antibody in the plate for 60 min at 37°C. The plates were washed three times with 0.3 ml of 0.1% Tween-20 in PBS. The non-specific interaction of unrelated proteins (e.g., serum peptides that may interfere with the analysis) with the antibody was reduced by incubating the pre-treated wells with a solution of 0.5% casein or 0.5% gelatin in PBS for 30 min at 37°C. Wells were washed with 0.1% Tween-20 in PBS prior to analysis of media samples.

The conditioned media were diluted 1:20 in 0.95 ml of 0.1% CHAPS in PBS. Media samples (50 or 100 μl/well) or α-sAPP standards (100 μl/well) in a range of about 3 to 30 ng/ml were added to the wells for a 60 min incubation at 37°C. The solution was then removed and each sample well was washed as described above. A horseradish peroxidase-conjugated goat affinity purified antibody raised against human $sAPP_{695}$ (designated polycab #1) was diluted in 0.1% Tween-20 in

PBS plus 10% normal rabbit serum and added to the wells as the signal antibody. The plates were incubated for 1 to 2 hr at 37°C and then washed to remove unbound antibody. The chromogenic substrate K-Blue Solution (Elisa Technologies, Lexington KY) was added to the wells (0.1 ml/well) and allowed to incubate for 15 min at ambient temperature. The reactions were stopped by addition of 0.1 ml of a 9.8% solution of phosphoric acid. The optical density of the samples was measured by spectrophotometry at 450 nm. The concentration of α-sAPP in the media was estimated from the α-sAPP standard curve. Samples were analyzed in duplicate.

EXAMPLE 30

A METHOD OF DETECTING AN INDICATOR OF ALZHEIMER'S DISEASE

Total s-APP and α-sAPP levels in cerebrospinal fluid (CSF) of normal subjects and members of a Swedish family carrying mutations of the APP gene at codons 670 and 671 ($APP_{670/671}$) were measured and compared. The $APP_{670/671}$ mutation in the Swedish family is associated with a high incidence of early onset Alzheimer's disease (AD). The clinical diagnosis of AD in the Swedish family harboring the mutation was based on NINCDS-ADRDA criteria [McKhann, et al. (1984) <u>Neurology</u> <u>34</u>:939-944]. The diagnosis was confirmed by neuropathologic examination of the brain of one deceased mutation carrier [Lannfelt, et al. (1994) <u>Neurosci. Lett.</u> <u>168</u>:254-256]. Cognitive functioning was assessed with the Mini Mental State Examination (MMSE) [Folstein, et al. (1975) <u>J. Psychiatry Res.</u> <u>12</u>:189-198]. The presence or absence of the $APP_{670/671}$ mutation was determined by polymerase chain reaction (PCR) nucleic acid amplification and restriction enzyme digestion according to a previously established procedure [Lannfelt, et al. (1993) <u>Neurosci. Lett.</u> <u>153</u>:85-87].

Lumbar CSF was obtained from eight normal non-carriers in the family, two presymptomatic healthy mutation carriers, and four mutation

carriers clinically symptomatic for AD. CSF samples were placed on ice, aliquoted and stored at -20°C until tested.

A. Measurement of APP Levels

Total sAPP and α-sAPP levels in the CSF samples were quantitated using a sandwich enzyme-linked immunosorbent assay (ELISA) and immunoblotting followed by laser-scanning densitometry, respectively.

Standards used in the assays were obtained by isolation of total sAPP and α-sAPP from medium conditioned by human neuroblastoma IMR32 cells [ATCC Accession No. CCL127] or the HGB695 cells, described above in Example 29B, as follows. Conditioned medium was filtered to remove large cell debris, and sAPP was extracted by passing the media over an anion exchange column using Toyopearl DEAE 650C resin (Toso-Hass, Philadelphia, PA). The bound sAPP was eluted from the column using a linear gradient of 0 to 0.6 M NaCl in 50 mM sodium phosphate, pH 7.5. All sAPP-containing eluate fractions were pooled and loaded onto an immunoaffinity column containing either a monoclonal antibody that specifically recognizes an amino-terminal epitope of human APP, such as, for example, monoclonal antibody P2-1 raised against native human P*N*-2 [see, e.g., U.S. Patent No. 5,213,962] or goat polyclonal polycab#1 raised against sAPP. linked to Toyopearl AF-Tresyl 650 M resin (Toso-Hass). Bound sAPP was eluted from the column with 0.1 M sodium citrate, pH 2.0. To separate α-sAPP from the other soluble forms of sAPP contained in total sAPP that do not contain at least the amino-terminal portion of Aβ, the total sAPP was loaded onto a Sepharose 4B immunoaffinity adsorption column containing a monoclonal antibody that recognizes an epitope within the first ~17 amino acids of Aβ (for example, monoclonal antibody 6E10). Specifically bound α-sAPP was eluted from the column with 0.1 M sodium citrate, pH 3.0. The solution pH of the purified sAPPs was adjusted to 7.2 and 1-ml aliquots were stored at -70°C.

B. Quantitation of Total sAPP

The ELISA used to quantitate total sAPP levels in CSF samples employed either a monoclonal antibody, such as P2-1, discussed above, that specifically recognizes an amino-terminal epitope of human APP, or a polyclonal antibody, such as goat polyclonal polycab#1, described above, as the capture antibody. The capture antibody was attached to the wells of a 96-well microtiter plate by incubating the plate with the antibody (that had been diluted in PBS, pH 7.2) for 60 min at 37°C. The plates were then washed three times with 0.3 ml of 0.1% Tween-20 in PBS. The wells were also incubated with a solution of 0.5% casein or 0.5% gelatin in PBS (150-200 μl/well) for 30 min. at 37 ° C.

CSF samples (50-100 μl diluted 1:20) or sAPP standards (50-100 μl) containing a range of 5 to 50 ng/ml were added to the wells and allowed to incubate for 60 min at 37°C. Following incubation, the wells were washed thoroughly with 0.1% Tween-20 in PBS. A goat anti-human APP polyclonal antibody raised against immunopurified APP from medium conditioned by cultured IMR32 human neuroblastoma cells (American Type Culture Collection Accession No. 127) conjugated to horseradish peroxidase was used as the signal antibody. The antibody was diluted 1:500 in PBS and 10% normal goat serum, pH 7.2, containing 0.1% Tween-20, added to the wells, and incubated for 60 min at 37 ° C. Unbound antibody was removed by washing as described above. To detect the bound antibody, 0.1 ml of the chromogenic substrate K-Blue Solution (Elisa Technologies, Lexington KY) was added to the wells and allowed to incubate for 15 min at ambient temperature. Reactions were stopped by addition of 0.1 ml of a 9.8% solution of phosphoric acid. The optical density of the samples was measured by spectrophotometry at 450 nm. The concentration of sAPP peptides in the CSF sample was estimated from the standard curve. Samples were analyzed in duplicate.

Total sAPP levels were also measured using quantitative immunoblotting essentially as described below for measurement of α-sAPP, except using a monoclonal antibody raised against a recombinant APP-containing fusion protein (e.g., 22C11 available from Boehringer Mannheim, Indianapolis, IN) at a concentration of 0.3 μg/ml to specifically detect sAPP and using purified sAPP as a standard. Quantification of total sAPP by quantitative immunoblot gave a 95% correlation to quantification by ELISA.

C. **Quantitation of α-sAPP**

For immunoblot assays of α-sAPP contained in the CSF samples, 5-10 μl of sample and purified standard α-sAPP of known concentrations were analyzed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) under reducing conditions. Samples were diluted into Laemmli sample buffer and loaded onto 7.5% SDS-PAGE gel. After separation, the proteins were transferred to polyvinylidene difluoride membranes (PVDF Immobilon, Millipore, Bedford, MA) in CAPS transfer buffer (5 mM 3-[cyclohexylamine]-1-propanesulfonic acid, pH 11.0, 5% (v/v) methanol). Nonspecific binding of protein to membranes was blocked with PBS containing 5% (w/v) non-fat dried milk and then incubated for 1 hr with a monoclonal antibody (20ml of 0.2 μg/ml) directed against the amino-terminus of Aβ (e.g., 6E10), and washed three times for one min each time in 20 ml of PBS and 0.1% Tween. Specifically bound antibody was detected using a biotinylated goat anti-mouse secondary antibody (Sigma) and a streptavidin-peroxidase conjugate (Amersham, Arlington Heights, IL) in combination with an enhanced chemiluminescence detection system (Amersham, Arlington Heights, IL). The blots were exposed to Kodak Scientific Imaging film X-OMAT AR and developed using a Kodak X-OMAT developer. Quantitation of the α-sAPP protein in the blots was performed by laser-scanning densitometry. Developed films within the linear range (or

multiple exposures) were scanned at 50 μM pixel size using a densitometer (Molecular Dynamics, Sunnyvale, CA), and the data were quantified using the ImageQuaNT software system (Molecular Dynamics). Quantified volumes of α-sAPP standard were used to generate standard curves. From the standard curves, the levels of α-sAPP in ng/ml were determined.

D. Comparison of sAPP and α-sAPP Levels in CSF of Normal Subjects and Mutation Carriers

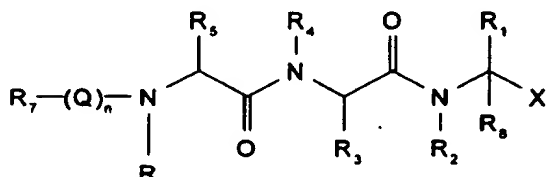
Assays of sAPP and α-sAPP levels in CSF from normal subjects and Swedish mutation carriers were performed. Mann-Whitney non-parametric statistics were used for comparison of the data from the experimental groups. Correlations were investigated with Pearson's and Spearman's rank correlation coefficients. Significance levels were set at $p<0.05$. The CSF of diseased carriers had lower levels of α-sAPP than the CSF samples of non-carriers, with no overlap between the two groups ($z=-2.72$; $p=0.007$). The CSF obtained from the four AD subjects had lower levels of α-sAPP than that of the two pre-symptomatic AD carriers. There was a strong inverse correlation between α-sAPP concentration and age in the mutation carriers ($R=0.94$; $p=0.005$). In the mutation carriers, ~25% of the total sAPP in CSF was α-sAPP compared to 33% in CSF of non-carriers. This was a statistically significant difference.

The results indicate that α-sAPP and the ratio of α-sAPP to total sAPP in CSF are useful markers in the detection of neurodegenerative disorders characterized by cerebral deposition of amyloid (e.g., AD) and in monitoring the progression of such disease. Furthermore, this assay system can be used in monitoring therapeutic intervention of these diseases.

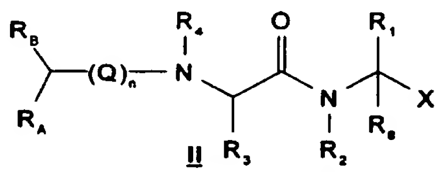
Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

CLAIMS:

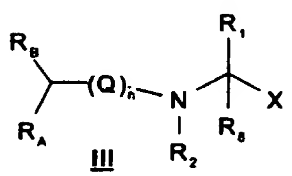
1. A method for inhibiting a protease, comprising contacting cells with a protease inhibiting amount of a compound of formula (I), (II) or (III):



I



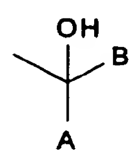
II



III

or the hydrates and isosteres, diastereomeric isomers and mixtures thereof, or pharmaceutically acceptable salts, wherein,

X has the formula:



in which A and B are each independently selected from the group consisting of H, halogen, alkyl, heterocycle, arylalkyl, haloalkyl, in which the alkyl groups are straight or branched chains or form a ring or fused rings,alkylhaloaryl, $(CH_2)_rCHN_2$, $CH_2(CH_2)_rOR_D$, $CH_2(CH_2)_rOZ_D$, $-(CH_2)_{r+1}W$, $-(CH_2)_{r+1}U$, preferably at least one of A or B is H;

r is 0-5;

the alkyl, aryl, carbocyclic and heterocyclic portions of X are unsubstituted or are substituted with one or more substituents independently selected from G;

G is halogen, preferably F, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR';

R and R' are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3;

the aryl groups preferably contain from 5-6 members and are unsubstituted or substituted with one or more substituents independently selected from G, which is preferably halogen, more preferably fluoro;

the heterocyclic rings preferably contain one or two heteroatoms and preferably contain 5 or 6 members;

Z_D is haloalkyl, in which the alkyl portion is straight or branched, cyclic, or mixtures thereof, the straight or branched chains contain from 1 to about 10, preferably 1-8, more preferably 1-6, most preferably 1-3, carbons in the chain, and the cyclic portions contain from 3 to about 10, preferably 3-7, carbons in the cycle, and the halo portion is preferably fluoro;

U is $-OR_D$ or $-NR_DR_E$;

R_D and R_E are each independently selected from among H, alkyl, preferably lower alkyl, more preferably C_{1-4} alkyl, phenyl, and phenethyl;

W is $-OR_D$, $-SR_D$, and $-NR_DR_E$, or a heterocyclic moiety, preferably containing 4-6, more preferably 5 or 6 members in the ring, and preferably one or two heteroatoms, selected from O, S, or N, in the ring

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi), or (vii) as follows:

(i) R_1, R_3, R_5, and R_8, are each independently selected from a side chain of a naturally occurring α-amino acid, H, alkyl, preferably lower (C_{1-6}) alkyl, alkenyl, preferably C_{2-10} alkenyl, alkynyl, preferably C_{2-6} alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl,

heteroaralkyl, heteroaralkenyl, Y-substituted aryl, aralkyl, aralkenyl, aralkynyl, and Z-substituted heteroaryl, heteroaralkyl, heteroaralkenyl, in which Y is selected from halogen, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR', R and R' are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3, Z is lower alkyl, preferably C_{1-4} alkyl, or halo lower alkyl, preferably C_{1-4} haloalkyl, more preferably CF_3;

R_2, R_4, R_6, and R_8 are each independently selected from among H and lower alkyl, preferably C_{1-4} alkyl;

R_7 is selected from among C_{1-6} alkyl, aryl, alkenyl, 9-fluoroenyl, aralkyl, aralkenyl, aralkynyl the aryl groups are unsubstituted or are substituted with Z;

Q is selected from among -C(O)-, -O-C(O)-, -C(O)O, $-S(O)_2$- and HN-C(O)-;

n is zero or one;

R_A is -$(T)_m$-$(D)_m$-R_1 in which T is O or NH, and D is C_{1-4} alkyl or C_{2-4} alkene; and m is zero or one; or

(ii) R_1, R_2, R_3, R_4, R_5, and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH;

n is zero; and

R_6 and R_7 are selected so that with the atoms to which each is attached they form a heterocyclic moiety, which:

(a) contains from 3 to 21 members and one or two or more fused rings, each ring containing preferably 3 to 7, more preferably 4 to 6, members, and is preferably morpholino, thiomorpholino, pyrrolidinyl, V-substituted pyrrolidinyl,

particularly 4-hydroxy pyrrolidinyl, or a reduced isoquinoline, preferably 1,2,3,4,tetrahydroisoquinoline;

(b) does not contain adjacent heteroatoms;

(c) is unsubstituted or substituted with one or more substituents selected from Y, more preferably from V, and most preferably selected from among OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH; or

(iii) R_1, R_2, R_3, R_4, R_5 and R_8 are selected as in (i);

V is as defined in (ii);

Q is C(O);

n is one; and

R_6 and R_7 are each independently selected as follows:

(a) from carbonyl (C=O), phenyl, a heteroatom, lower alkyl, preferably C_{1-3} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-3} alkyl, and

(b) each is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a cyclic moiety, preferably a 4-6 membered cyclic or 8-12 membered bicylic moiety, and

(d) R_6 and R_7 are selected with the proviso that when two or more heteroatoms are present there is a carbon atom between the heteroatoms; and

(e) the cyclic moiety is preferably succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_B, Q and n are as defined in any of (i)-(iii) or (v)-(vii),

V is as defined in (ii);

R_8 is H; and

R_1 and R_2 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_1 and R_2 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, Q and n are as defined in any of (i)-(iv) or (vi)-(vii);

V is as defined in (ii);

R_3 and R_4 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl;

(vi) R_1, R_2, R_3, R_4, R_7, R_8, Q and n are as defined in any of (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

R_5 and R_6 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_6 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6 and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

n is zero; and

R_5 and R_7 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_7 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl.

2. The method of claim 1, wherein X is selected from $(CH_2)_{r+1}C(OH)$halo-substituted alkyl or CH(OH)halo-substituted alkyl, preferably $-CH(OH)C_kH_{(2k+1-s)}F_s$ in which k is 1-6, preferably 1-3, s is 0 to 2k+1; $-CH(OH)C_6H_{(5-q)}F_q$ in which q is 0 to 5; $-(CH_2)_{r+1}C(OH)CF_3$, $-CH(OH)CF_3$, $-(CH_2)_{r+1}C(OH)C_2F_5$, $-CH(OH)C_2F_5$, $-(CH_2)_{r+1}C(OH)H$, -CH(OH)H, $-(CH_2)_{r+1}C(OH)(CH_2)_rCHN_2$, $-CH(OH)(CH_2)_rCHN_2$, $-(CH_2)_{r+1}C(OH)$haloalkyl, -CH(OH)haloalkyl, $-(CH_2)_{r+1}C(OH)(CH_2)_rU$, $-CH(OH)(CH_2)_rU$, $-(CH_2)_{r+1}C(OH)CH_2W$ and -CH(OH)haloaryl, and more preferably $-CH(OH)CF_3$ or $-CH(OH)C_2F_5$.

3. The method of claim 1 or claim 2, wherein:

R_1 is H or a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated, preferably a double bond, or is cyclic moiety containing from 5 to 6 members, and is more preferably methyl, 2-methyl propene, 2-butene, cyclohexyl, lower alkyl-substituted cyclohexyl or cyclohexylmethyl, hydroxyphenyl, isopropyl, toluyl, t-butyl, isobutyl, n-butyl, 1-aminobutyl, methylethylthioether and is more preferably n-butyl, toluyl, isobutyl or cyclohexylmethyl;

R_2, R_4 and R_8 are each independently selected from among H or C_{1-4} alkyl, and more preferably methyl or ethyl;

R_3 is H, C_{1-4} alkyl, aryl, particularly phenyl, naphthyl and hydroxyphenyl, 1-aminobutyl, acetamide, and more preferably *iso*-butyl, benzyl, phenyl or toluyl;

R_5 is C_{1-4} alkyl, and more preferably *iso*-butyl;

R_6 is H or C_{1-4} alkyl, and more preferably H or methyl;

R_7 - $(Q)_n$ is acyl (Ac), benzyloxycarbonyl (Cbz), 9-fluorenylmethylcarbonate (Fmoc), BOC, tosyl, with Cbz, Ac and Fmoc being more preferred, and Cbz and Ac most preferred;

Q is -C(O)-, $-S(O)_2-$ and -O-C(O)-, with -C(O)- and -O-C(O)- being more preferred, and -O-C(O)- most preferred;

R_8 is C_{1-4} alkyl or C_{2-4} alkenyl, and more preferably *iso*-butyl;

R_A is $-(T)_m-(D)_m-R_1$, in which T is oxygen or nitrogen, with oxygen being more preferred, and D is C_{1-4} alkyl or C_{2-4} alkenyl, with a mono-unsaturated C_{3-4} alkenyl being more preferred; and

X, which is as defined above, is preferably a secondary alcohol, and more preferably least one of A or B is H and the other is haloalkyl, in which the carbon chain is straight, branched or cyclic, and is preferably a lower alkyl containing 1-6 carbons, such as CF_3, C_2F_5.

4. The method of any of claims 1-3, wherein:

R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated bond,

R_2, R_4, and R_8 are each independently H, methyl or ethyl;

R_3 is *iso*-butyl, toluyl or phenyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is acetyl or benzyloxycarbonyl (Cbz);

Q is -C(O)- or -O-C(O);

R_8 is C_{1-4} alkyl or C_{2-4} alkenyl,;

$R_A = -(T)_m-(D)_m-R_1$, in which T is oxygen or carbon, and D is C_{2-4} alkenyl; and

X is a secondary alcohol.

5. The method of any of claims 1-4, wherein:

R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated bond,

R_2, R_4, and R_8 are each independently H, methyl or ethyl;

R_3 is *iso*-butyl, toluyl or phenyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is acetyl or benzyloxycarbonyl (Cbz);

Q is -C(O)- or -O-C(O);

R_8 is C_{1-4} alkyl or C_{2-4} alkenyl,;

R_A = $-(T)_m-(D)_m-R_1$, in which T is oxygen or carbon, and D is C_{2-4} alkenyl.

6. The method of any of claims 1-5, wherein X is $-CH(OH)CF_3$, $-CH(OH)C_2F_5$, $-(CH_2)_rCH(OH)C_kH_{(2k+1-s)}F_s$ in which k is 1-6 and s is 0 to 2k+1, or $-CH(OH)C_6H_{(5-q)}F_q$ in which q is 0 to 5;

the carbon or heterocyclic ring(s) contain from 5-7 members in the ring(s);

r is 0 to 3; and

all alkyl groups contain from 1 to 6 carbon atoms.

7. The method of any of claims 1-6, wherein:

R_8 is H; and

the heterocyclic ring moiety containing R_1 and R_2 and the atoms to which they are attached, is selected from among morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl.

8. The method of any of claims 1-6, wherein:

$(Q)_n$ is a carbonyl group; and

the heterocyclic ring moiety containing R_6 and R_7 and the atoms to which they are attached is selected from among succinimide, phthalimide or maleimide, and is preferably phthalimide.

9. The method of any of claims 1-6, wherein:

n is zero; and

the heterocyclic ring moiety containing R_6 and R_7 and the atoms to which they are attached is morpholino, thiomorpholino, pyrrolidinyl or V-substituted pyrrolidinyl.

10. The method of claim 9, wherein the heterocyclic ring moiety containing R_6 and R_7 is 4-hydroxy pyrrolidinyl or 1,2,3,4-tetrahydroisoquinoline.

11. The method of any of claims 1-6, wherein:

n is zero; and

R_3 and R_4 or R_5 and R_7 are taken together with the atoms to which they are attached form morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, preferably 4-hydroxy pyrrolidinyl.

12. The method of any of claims 1-6, wherein:

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi) or (vii) as follows:

(i) R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated a double bond, or is cyclic moiety containing from 5 to 6 members;

R_2, R_4, and R_8 are each independently selected from methyl or ethyl or propyl;

R_3 is selected from the group consisting of C_{1-4} alkyl, phenyl, naphthyl, hydroxyphenyl, 1-aminobutyl, acetamide and *iso*-butyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is selected from the group consisting of acetyl, benzyloxycarbonyl (Cbz), 9-fluorenylmethylcarbonate (Fmoc), Ac, BOC and tosyl;

Q is -C(O)-, -S(O)$_2$- or -O-C(O);

R_B is C_{1-4} alkyl or C_{2-4} alkenyl;

R_A = -$(T)_m$-$(D)_m$-R_1, in which T is oxygen, carbon, or nitrogen, and D is C_{1-4} alkyl or C_{2-4} alkenyl; or

(ii) R_1, R_2, R_3, R_4, R_5, R_8, R_A, Y and R_B are selected as in (i), (iv) or (v);

V is OH or halogen;

n is zero; and

R_6 and R_7 together with the atoms to which each is attached

form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, 4-hydroxy pyrrolidinyl and 1,2,3,4,tetrahydroisoquinoline; or

(iii) R_1, R_2, R_3, R_4, R_5, R_8, R_A and R_B are selected as in (i);

V is as defined in (ii);

Q is C(O);

n is one; and

R_6 and R_7 together with the atoms to which each is attached form succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_B, Q and n are as defined in any of (i)-(iii) or (v)-(viii),

V is as defined in (ii);

R_8 is H; and

R_1 and R_2 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, R_A, R_B Q and n are as defined in any of (i)-(iv) or (vi)-(viii);

V is as defined in (ii);

R_3 and R_4 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(vi) R_1, R_2, R_3, R_4, R_7, R_8, R_A, R_B, Q and n are as defined in any of (i), (iv) or (v);

V is as defined in (ii);

R_5 and R_6 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6, R_8, R_A and R_B are selected as in (i) (iv) or (v);

V is as defined in (ii);

n is zero; and

R_5 and R_7 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl.

13. The method of claim 12, wherein at least one of R_1, R_3, and R_5 are selected from the group consisting of C_{2-6} alkenyl and C_{2-6} alkynyl.

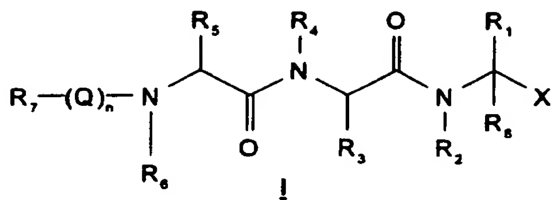
14. The method of claim 12 or claim 13, wherein at least one of R_1, R_3, and R_5 are selected from the group consisting of 2-methyl-propene, 2-butene, cyclohexylglycine and cyclohexylalanine.

15. The method of claim 1, wherein the compound is selected from (2*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (1*SR*)-(2*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[1-(thiazole-hexanol)]amide, (2*SR*)-*N*-Cbz-1,1,1-trifluoro-2-heptanol, (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Pro-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-HydroxyPro-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Pro-L-Leu *N*-[3-(1,1,1-trifluoro-2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-HydroxyPro-L-Leu *N*-[3-(1,1,1-trifluoro-2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*SR*)-*N*-valeroyl-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-4-phenyl-2-butanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-4-cyclohexyl-2-butanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-3-phenyl-2-propanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-3-cyclohexyl-2-propanol)]amide, (2*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-butanol)]amide, (3*SR*)-(4S)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(ethyl 2,2-difluoro-3-hydroxyoctanoate)]amide, (4*S*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-octanol)]amide, (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-methyl-3-octanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-

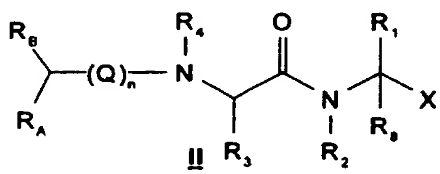
methyl-2-heptanol)]amide, (2*SR*)-H-L-Leu *N*-[2-(ethyl 4-methyl-4-pentenoate)]amide hydrochloride, (2*SR*)-*N*-[(2*S*)-2-benzoxy-4-methylpentanoyl]-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-Leu *N*-[3-(2-hydroxy-heptanoic acid)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(methyl 2-hydroxy-heptanoate)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(benzyl 2-hydroxy-heptamide)]amide, (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(benzyl 3-hydroxy-octamide)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu N-[3-(1-furfylthio-2-heptanol)]amide, (2*SR*)-*N*-[(2*R*)-[2-(1'-phenyl-1'-propene)-4-methylpentanoyl]]-L-Leu-*N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-*N*-Ac-L-Leu-L-Leu-*N* [2-(trans-4-hexanol)]amide, (2*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, *N*-dansyl-L-Leu-L-Leu-DL-norleucinol, and *N*-Ac-L-Phe-L-Leu-DL-norleucinol.

16. The method of claim 1, wherein the compound is seleted from (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide and (2*SR*)-(3*SR*)-*N*-valeroyl-L-Leu *N*-[3-(1 ,1,1-trifluoro-2-heptanol)]amide.

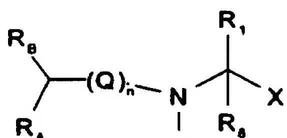
17. A method of modulating the processing of amyloid precursor protein (APP), comprising contacting the APP with a compound of formula (I), (II) or (III):



I



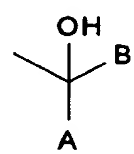
II



III

or the hydrates and isosteres, diastereomeric isomers and mixtures thereof, or pharmaceutically acceptable salts, wherein,

X has the formula:



in which A and B are each independently selected from the group consisting of H, halogen, alkyl, heterocycle, arylalkyl, haloalkyl, in which the alkyl groups are straight or branched chains or form a ring or fused rings,alkylhaloaryl, $(CH_2)_rCHN_2$, $CH_2(CH_2)_rOR_D$, $CH_2(CH_2)_rOZ_D$, $-(CH_2)_{r+1}W$, $-(CH_2)_{r+1}U$, preferably at least one of A or B is H;

r is 0-5;

the alkyl, aryl, carbocyclic and heterocyclic portions of X are unsubstituted or are substituted with one or more substituents independently selected from G;

G is halogen, preferably F, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR';

R and R' are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3;

the aryl groups preferably contain from 5-6 members and are unsubstituted or substituted with one or more substituents independently selected from G, which is preferably halogen, more preferably fluoro;

the heterocyclic rings preferably contain one or two heteroatoms and preferably contain 5 or 6 members;

Z_D is haloalkyl, in which the alkyl portion is straight or branched, cyclic, or mixtures thereof, the straight or branched chains contain from 1 to about 10, preferably 1-8, more preferably 1-6, most preferably 1-3, carbons in the chain, and the cyclic portions contain from 3 to about 10, preferably 3-7, carbons in the cycle, and the halo portion is preferably fluoro;

U is $-OR_D$ or $-NR_DR_E$;

R_D and R_E are each independently selected from among H, alkyl, preferably lower alkyl, more preferably C_{1-4} alkyl, phenyl, and phenethyl;

W is $-OR_D$, $-SR_D$, and $-NR_DR_E$, or a heterocyclic moiety, preferably containing 4-6, more preferably 5 or 6 members in the ring, and preferably one or two heteroatoms, selected from O, S, or N, in the ring

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi), or (vii) as follows:

(i) R_1, R_3, R_5, and R_8, are each independently selected from a side chain of a naturally occurring α-amino acid, H, alkyl, preferably lower (C_{1-6}) alkyl, alkenyl, preferably C_{2-10} alkenyl, alkynyl, preferably C_{2-6} alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, Y-substituted aryl, aralkyl, aralkenyl, aralkynyl, and Z-substituted heteroaryl, heteroaralkyl, heteroaralkenyl, in which Y is selected from halogen, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR', R and R' are independently selected from H or alkyl,

preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3, Z is lower alkyl, preferably C_{1-4} alkyl, or halo lower alkyl, preferably C_{1-4} haloalkyl, more preferably CF_3;

R_2, R_4, R_6, and R_8 are each independently selected from among H and lower alkyl, preferably C_{1-4} alkyl;

R_7 is selected from among C_{1-6} alkyl, aryl, alkenyl, 9-fluoroenyl, aralkyl, aralkenyl, aralkynyl the aryl groups are unsubstituted or are substituted with Z;

Q is selected from among -C(O)-, -O-C(O)-, -C(O)O, —$S(O)_2$- and HN-C(O)-;

n is zero or one;

R_A is -$(T)_m$-$(D)_m$-R_1 in which T is O or NH, and D is C_{1-4} alkyl or C_{2-4} alkene; and m is zero or one; or

(ii) R_1, R_2, R_3, R_4, R_5, and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH;

n is zero; and

R_6 and R_7 are selected so that with the atoms to which each is attached they form a heterocyclic moiety, which:

(a) contains from 3 to 21 members and one or two or more fused rings, each ring containing preferably 3 to 7, more preferably 4 to 6, members, and is preferably morpholino, thiomorpholino, pyrrolidinyl, V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl, or a reduced isoquinoline, preferably 1,2,3,4,tetrahydroisoquinoline;

(b) does not contain adjacent heteroatoms;

(c) is unsubstituted or substituted with one or more substituents selected from Y, more preferably from V, and

most preferably selected from among OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH; or

(iii) R_1, R_2, R_3, R_4, R_5 and R_8 are selected as in (i);

V is as defined in (ii);

Q is C(O);

n is one; and

R_6 and R_7 are each independently selected as follows:

(a) from carbonyl (C=O), phenyl, a heteroatom, lower alkyl, preferably C_{1-3} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-3} alkyl, and

(b) each is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a cyclic moiety, preferably a 4-6 membered cyclic or 8-12 membered bicylic moiety, and

(d) R_6 and R_7 are selected with the proviso that when two or more heteroatoms are present there is a carbon atom between the heteroatoms; and

(e) the cyclic moiety is preferably succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_8, Q and n are as defined in any of (i)-(iii) or (v)-(vii),

V is as defined in (ii);

R_8 is H; and

R_1 and R_2 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_1 and R_2 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, Q and n are as defined in any of (i)-(iv) or (vi)-(vii);

V is as defined in (ii);

R_3 and R_4 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl;

(vi) R_1, R_2, R_3, R_4, R_7, R_8, Q and n are as defined in any of (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

R_5 and R_6 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_6 and R_8 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6 and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

n is zero; and

R_5 and R_7 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_7 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl.

18. The method of claim 17, wherein X is selected from $(CH_2)_{r+1}C(OH)$halo-substituted alkyl or $CH(OH)$halo-substituted alkyl, preferably $-CH(OH)C_kH_{(2k+1-s)}F_s$ in which k is 1-6, preferably 1-3, s is 0 to 2k+1; $-CH(OH)C_6H_{(5-q)}F_q$ in which q is 0 to 5; $-(CH_2)_{r+1}C(OH)CF_3$, $-CH(OH)CF_3$, $-(CH_2)_{r+1}C(OH)C_2F_5$, $-CH(OH)C_2F_5$, $-(CH_2)_{r+1}C(OH)H$, $-CH(OH)H$, $-(CH_2)_{r+1}C(OH)(CH_2)_rCHN_2$, $-CH(OH)(CH_2)_rCHN_2$, $-(CH_2)_{r+1}C(OH)$haloalkyl, $-CH(OH)$haloalkyl, $-(CH_2)_{r+1}C(OH)(CH_2)_rU$,

$-CH(OH)(CH_2)_rU$, $-(CH_2)_{r+1}C(OH)CH_2W$ and -CH(OH)haloaryl, and more preferably $-CH(OH)CF_3$ or $-CH(OH)C_2F_5$.

19. The method of claim 17 or claim 18, wherein:

R_1 is H or a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated, preferably a double bond, or is cyclic moiety containing from 5 to 6 members, and is more preferably methyl, 2-methyl propene, 2-butene, cyclohexyl, lower alkyl-substituted cyclohexyl or cyclohexylmethyl, hydroxyphenyl, isopropyl, toluyl, t-butyl, isobutyl, n-butyl, 1-aminobutyl, methylethylthioether and is more preferably n-butyl, toluyl, isobutyl or cyclohexylmethyl;

R_2, R_4 and R_8 are each independently selected from among H or C_{1-4} alkyl, and more preferably methyl or ethyl;

R_3 is H, C_{1-4} alkyl, aryl, particularly phenyl, naphthyl and hydroxyphenyl, 1-aminobutyl, acetamide, and more preferably *iso*-butyl, benzyl, phenyl or toluyl;

R_5 is C_{1-4} alkyl, and more preferably *iso*-butyl;

R_6 is H or C_{1-4} alkyl, and more preferably H or methyl;

R_7 - $(Q)_n$ is acyl (Ac), benzyloxycarbonyl (Cbz), 9-fluorenylmethylcarbonate (Fmoc), BOC, tosyl, with Cbz, Ac and Fmoc being more preferred, and Cbz and Ac most preferred;

Q is -C(O)-, $-S(O)_2-$ and -O-C(O)-, with -C(O)- and -O-C(O)- being more preferred, and -O-C(O)- most preferred;

R_B is C_{1-4} alkyl or C_{2-4} alkenyl, and more preferably *iso*-butyl;

R_A is $-(T)_m-(D)_m-R_1$, in which T is oxygen or nitrogen, with oxygen being more preferred, and D is C_{1-4} alkyl or C_{2-4} alkenyl, with a mono-unsaturated C_{3-4} alkenyl being more preferred; and

X, which is as defined above, is preferably a secondary alcohol, and more preferably least one of A or B is H and the other is haloalkyl, in which the carbon chain is straight, branched or cyclic, and is preferably a lower alkyl containing 1-6 carbons, such as CF_3, C_2F_5.

20. The method of any of claims 17-19, wherein:

R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated bond,

R_2, R_4, and R_8 are each independently H, methyl or ethyl;

R_3 is *iso*-butyl, toluyl or phenyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is acetyl or benzyloxycarbonyl (Cbz);

Q is -C(O)- or -O-C(O);

R_B is C_{1-4} alkyl or C_{2-4} alkenyl,;

R_A = $-(T)_m-(D)_m-R_1$, in which T is oxygen or carbon, and D is C_{2-4} alkenyl; and

X is a secondary alcohol.

21. The method of any of claims 17-20, wherein:

R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated bond,

R_2, R_4, and R_8 are each independently H, methyl or ethyl;

R_3 is *iso*-butyl, toluyl or phenyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is acetyl or benzyloxycarbonyl (Cbz);

Q is -C(O)- or -O-C(O);

R_B is C_{1-4} alkyl or C_{2-4} alkenyl,;

R_A = $-(T)_m-(D)_m-R_1$, in which T is oxygen or carbon, and D is C_{2-4} alkenyl.

22. The method of any of claims 17-21, wherein X is $-CH(OH)CF_3$, $-CH(OH)C_2F_5$, $-(CH_2)_rCH(OH)C_kH_{(2k+1-s)}F_s$ in which k is 1-6 and s is 0 to 2k+1, or $-CH(OH)C_6H_{(5-q)}F_q$ in which q is 0 to 5;

the carbon or heterocyclic ring(s) contain from 5-7 members in the ring(s);

r is 0 to 3; and

all alkyl groups contain from 1 to 6 carbon atoms.

23. The method of any of claims 17-22, wherein:

R_8 is H; and

the heterocyclic ring moiety containing R_1 and R_2 and the atoms to which they are attached, is selected from among morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl.

24. The method of any of claims 17-22, wherein:

$(Q)_n$ is a carbonyl group; and

the heterocyclic ring moiety containing R_6 and R_7 and the atoms to which they are attached is selected from among succinimide, phthalimide or maleimide, and is preferably phthalimide.

25. The method of any of claims 17-22, wherein:

n is zero; and

the heterocyclic ring moiety containing R_6 and R_7 and the atoms to which they are attached is morpholino, thiomorpholino, pyrrolidinyl or V-substituted pyrrolidinyl.

26. The method of claim 25, wherein the heterocyclic ring moiety containing R_6 and R_7 is 4-hydroxy pyrrolidinyl or 1,2,3,4-tetrahydroisoquinoline.

27. The method of any of claims 17-22, wherein:

n is zero; and

R_3 and R_4 or R_5 and R_7 are taken together with the atoms to which they are attached form morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, preferably 4-hydroxy pyrrolidinyl.

28. The method of any of claims 17-22, wherein:

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi) or (vii) as follows:

(i) R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated a double bond, or is cyclic

moiety containing from 5 to 6 members;

R_2, R_4, and R_8 are each independently selected from methyl or ethyl or propyl;

R_3 is selected from the group consisting of C_{1-4} alkyl, phenyl, naphthyl, hydroxyphenyl, 1-aminobutyl, acetamide and *iso*-butyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is selected from the group consisting of acetyl, benzyloxycarbonyl (Cbz), 9-fluorenylmethylcarbonate (Fmoc), Ac, BOC and tosyl;

Q is -C(O)-, -S(O)$_2$- or -O-C(O);

R_B is C_{1-4} alkyl or C_{2-4} alkenyl;

R_A = $-(T)_m-(D)_m-R_1$, in which T is oxygen, carbon, or nitrogen, and D is C_{1-4} alkyl or C_{2-4} alkenyl; or

(ii) R_1, R_2, R_3, R_4, R_5, R_8, R_A, Y and R_B are selected as in (i), (iv) or (v);

V is OH or halogen;

n is zero; and

R_6 and R_7 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, 4-hydroxy pyrrolidinyl and 1,2,3,4,tetrahydroisoquinoline; or

(iii) R_1, R_2, R_3, R_4, R_5, R_8, R_A and R_B are selected as in (i);

V is as defined in (ii);

Q is C(O);

n is one; and

R_6 and R_7 together with the atoms to which each is attached form succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_B, Q and n are as defined in any

of (i)-(iii) or (v)-(viii),

V is as defined in (ii);

R_8 is H; and

R_1 and R_2 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, R_A, R_B Q and n are as defined in any of (i)-(iv) or (vi)-(viii);

V is as defined in (ii);

R_3 and R_4 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(vi) R_1, R_2, R_3, R_4, R_7, R_8, R_A, R_B, Q and n are as defined in any of (i), (iv) or (v);

V is as defined in (ii);

R_5 and R_6 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6, R_8, R_A and R_B are selected as in (i) (iv) or (v);

V is as defined in (ii);

n is zero; and

R_5 and R_7 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl.

29. The method of claim 28, wherein at least one of R_1, R_3, and R_5 are selected from the group consisting of C_{2-6} alkenyl and C_{2-6} alkynyl.

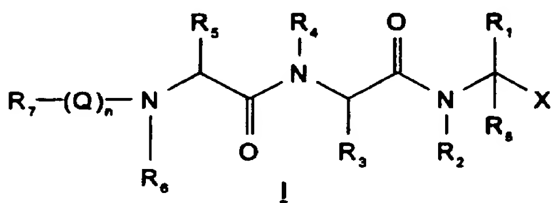
30. The method of claim 28 or claim 29, wherein at least one of R_1, R_3, and R_5 are selected from the group consisting of 2-methyl-propene, 2-butene, cyclohexylglycine and cyclohexylalanine.

31. The method of claim 17, wherein the compound is selected from (2*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (1*SR*)-(2*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[1-(thiazole-hexanol)]amide, (2*SR*)-*N*-Cbz-1,1,1-trifluoro-2-heptanol, (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Pro-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-HydroxyPro-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Pro-L-Leu *N*-[3-(1,1,1-trifluoro-2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-HydroxyPro-L-Leu *N*-[3-(1,1,1-trifluoro-2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*SR*)-*N*-valeroyl-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-4-phenyl-2-butanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-4-cyclohexyl-2-butanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-3-phenyl-2-propanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-3-cyclohexyl-2-propanol)]amide, (2*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-butanol)]amide, (3*SR*)-(4S)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(ethyl 2,2-difluoro-3-hydroxyoctanoate)]amide, (4*S*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-octanol)]amide, (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-methyl-3-octanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-methyl-2-heptanol)]amide, (2*SR*)-H-L-Leu *N*-[2-(ethyl 4-methyl-4-pentenoate)]amide hydrochloride, (2*SR*)-*N*-[(2*S*)-2-benzoxy-4-methylpentanoyl]-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-Leu *N*-[3-(2-hydroxy-heptanoic acid)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(methyl 2-hydroxy-heptanoate)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(benzyl 2-hydroxy-heptamide)]amide, (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(benzyl 3-hydroxy-octamide)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu N-[3-(1-furfylthio-2-heptanol)]amide, (2*SR*)-*N*-[(2*R*)-[2-(1'-phenyl-1'-propene)-4-methylpentanoyl]]-L-Leu-*N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-*N*-Ac-L-Leu-L-Leu-*N* [2-(trans-4-hexanol)]amide,

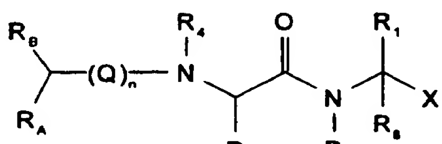
(*2SR*)-*N*-Ac-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (*2SR*)-*N*-Ac-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, *N*-dansyl-L-Leu-L-Leu-DL-norleucinol, and *N*-Ac-L-Phe-L-Leu-DL-norleucinol.

32. The method of claim 17, wherein the compound is seleted from (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide and (2*SR*)-(3*SR*)-*N*-valeroyl-L-Leu *N*-[3-(1 ,1,1-trifluoro-2-heptanol)]amide.

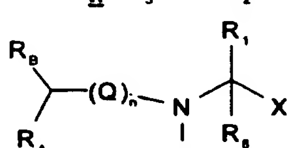
33. A method of treating a neurodegenerative disease that is characterized by the deposition of cerebral amyloid, comprising administering to a patient a therapeutically effective amount of a compound of formula (I), (II) or (III):



I



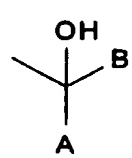
II



III

or the hydrates and isosteres, diastereomeric isomers and mixtures thereof, or pharmaceutically acceptable salts, wherein,

X has the formula:



in which A and B are each independently selected from the group consisting of H, halogen, alkyl, heterocycle, arylalkyl, haloalkyl, in which the alkyl groups are straight or branched chains or form a ring or fused rings,alkylhaloaryl, $(CH_2)_rCHN_2$, $CH_2(CH_2)_rOR_D$, $CH_2(CH_2)_rOZ_D$, $-(CH_2)_{r+1}W$, $-(CH_2)_{r+1}U$, preferably at least one of A or B is H;

r is 0-5;

the alkyl, aryl, carbocyclic and heterocyclic portions of X are unsubstituted or are substituted with one or more substituents independently selected from G;

G is halogen, preferably F, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR';

R and R' are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3;

the aryl groups preferably contain from 5-6 members and are unsubstituted or substituted with one or more substituents independently selected from G, which is preferably halogen, more preferably fluoro;

the heterocyclic rings preferably contain one or two heteroatoms and preferably contain 5 or 6 members;

Z_D is haloalkyl, in which the alkyl portion is straight or branched, cyclic, or mixtures thereof, the straight or branched chains contain from 1 to about 10, preferably 1-8, more preferably 1-6, most preferably 1-3, carbons in the chain, and the cyclic portions contain from 3 to about 10, preferably 3-7, carbons in the cycle, and the halo portion is preferably fluoro;

U is $-OR_D$ or $-NR_DR_E$;

R_D and R_E are each independently selected from among H, alkyl, preferably lower alkyl, more preferably C_{1-4} alkyl, phenyl, and phenethyl;

W is $-OR_D$, $-SR_D$, and $-NR_DR_E$, or a heterocyclic moiety, preferably containing 4-6, more preferably 5 or 6 members in the ring, and preferably one or two heteroatoms, selected from O, S, or N, in the ring

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi), or (vii) as follows:

(i) R_1, R_3, R_5, and R_B, are each independently selected from a side chain of a naturally occurring α-amino acid, H, alkyl, preferably lower (C_{1-6}) alkyl, alkenyl, preferably C_{2-10} alkenyl, alkynyl, preferably C_{2-6} alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, Y-substituted aryl, aralkyl, aralkenyl, aralkynyl, and Z-substituted heteroaryl, heteroaralkyl, heteroaralkenyl, in which Y is selected from halogen, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR', R and R' are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3, Z is lower alkyl, preferably C_{1-4} alkyl, or halo lower alkyl, preferably C_{1-4} haloalkyl, more preferably CF_3;

R_2, R_4, R_6, and R_8 are each independently selected from among H and lower alkyl, preferably C_{1-4} alkyl;

R_7 is selected from among C_{1-6} alkyl, aryl, alkenyl, 9-fluoroenyl, aralkyl, aralkenyl, aralkynyl the aryl groups are unsubstituted or are substituted with Z;

Q is selected from among -C(O)-, -O-C(O)-, -C(O)O, —$S(O)_2$- and HN-C(O)-;

n is zero or one;

R_A is $-(T)_m-(D)_m-R_1$ in which T is O or NH, and D is C_{1-4} alkyl or C_{2-4} alkene; and m is zero or one; or

(ii) R_1, R_2, R_3, R_4, R_5, and R_8 are selected as in (i),

(iv)(a-c) with R_8 being H or (v)(a-c);

V is OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH;

n is zero; and

R_6 and R_7 are selected so that with the atoms to which each is attached they form a heterocyclic moiety, which:

(a) contains from 3 to 21 members and one or two or more fused rings, each ring containing preferably 3 to 7, more preferably 4 to 6, members, and is preferably morpholino, thiomorpholino, pyrrolidinyl, V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl, or a reduced isoquinoline, preferably 1,2,3,4,tetrahydroisoquinoline;

(b) does not contain adjacent heteroatoms;

(c) is unsubstituted or substituted with one or more substituents selected from Y, more preferably from V, and most preferably selected from among OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH; or

(iii) R_1, R_2, R_3, R_4, R_5 and R_8 are selected as in (i);

V is as defined in (ii);

Q is C(O);

n is one; and

R_6 and R_7 are each independently selected as follows:

(a) from carbonyl (C=O), phenyl, a heteroatom, lower alkyl, preferably C_{1-3} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-3} alkyl, and

(b) each is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a cyclic moiety, preferably a 4-6 membered cyclic or 8-12 membered bicylic moiety, and

(d) R_6 and R_7 are selected with the proviso that when two or more heteroatoms are present there is a carbon atom between the heteroatoms; and

(e) the cyclic moiety is preferably succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_B, Q and n are as defined in any of (i)-(iii) or (v)-(vii),

V is as defined in (ii);

R_8 is H; and

R_1 and R_2 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_1 and R_2 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, Q and n are as defined in any of (i)-(iv) or (vi)-(vii);

V is as defined in (ii);

R_3 and R_4 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 mem-

bered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl;

(vi) R_1, R_2, R_3, R_4, R_7, R_8, Q and n are as defined in any of (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

R_5 and R_6 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_6 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6 and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

n is zero; and

R_5 and R_7 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_7 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are

attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl.

34. The method of claim 33, wherein X is selected from $(CH_2)_{r+1}C(OH)$halo-substituted alkyl or CH(OH)halo-substituted alkyl, preferably $-CH(OH)C_kH_{(2k+1-s)}F_s$ in which k is 1-6, preferably 1-3, s is 0 to 2k+1; $-CH(OH)C_6H_{(5-q)}F_q$ in which q is 0 to 5; $-(CH_2)_{r+1}C(OH)CF_3$, $-CH(OH)CF_3$, $-(CH_2)_{r+1}C(OH)C_2F_5$, $-CH(OH)C_2F_5$, $-(CH_2)_{r+1}C(OH)H$, -CH(OH)H, $-(CH_2)_{r+1}C(OH)(CH_2)_rCHN_2$, $-CH(OH)(CH_2)_rCHN_2$, $-(CH_2)_{r+1}C(OH)$haloalkyl, -CH(OH)haloalkyl, $-(CH_2)_{r+1}C(OH)(CH_2)_rU$, $-CH(OH)(CH_2)_rU$, $-(CH_2)_{r+1}C(OH)CH_2W$ and -CH(OH)haloaryl, and more preferably $-CH(OH)CF_3$ or $-CH(OH)C_2F_5$.

35. The method of claim 33 or claim 34, wherein:

R_1 is H or a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated, preferably a double bond, or is cyclic moiety containing from 5 to 6 members, and is more preferably methyl, 2-methyl propene, 2-butene, cyclohexyl, lower alkyl-substituted cyclohexyl or cyclohexylmethyl, hydroxyphenyl, isopropyl, toluyl, t-butyl, isobutyl, n-butyl, 1-aminobutyl, methylethylthioether and is more preferably n-butyl, toluyl, isobutyl or cyclohexylmethyl;

R_2, R_4 and R_8 are each independently selected from among H or C_{1-4} alkyl, and more preferably methyl or ethyl;

R_3 is H, C_{1-4} alkyl, aryl, particularly phenyl, naphthyl and hydroxyphenyl, 1-aminobutyl, acetamide, and more preferably *iso*-butyl, benzyl, phenyl or toluyl;

R_5 is C_{1-4} alkyl, and more preferably *iso*-butyl;

R_6 is H or C_{1-4} alkyl, and more preferably H or methyl;

R_7 - $(Q)_n$ is acyl (Ac), benzyloxycarbonyl (Cbz), 9-fluorenylmethylcarbonate (Fmoc), BOC, tosyl, with Cbz, Ac and Fmoc

being more preferred, and Cbz and Ac most preferred;

Q is -C(O)-, -S(O)$_2$- and -O-C(O)-, with -C(O)- and -O-C(O)- being more preferred, and -O-C(O)- most preferred;

R_B is C_{1-4} alkyl or C_{2-4} alkenyl, and more preferably *iso*-butyl;

R_A is $-(T)_m-(D)_m-R_1$, in which T is oxygen or nitrogen, with oxygen being more preferred, and D is C_{1-4} alkyl or C_{2-4} alkenyl, with a mono-unsaturated C_{3-4} alkenyl being more preferred; and

X, which is as defined above, is preferably a secondary alcohol, and more preferably least one of A or B is H and the other is haloalkyl, in which the carbon chain is straight, branched or cyclic, and is preferably a lower alkyl containing 1-6 carbons, such as CF_3, C_2F_5.

36. The method of any of claims 33-35, wherein:

R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated bond,

R_2, R_4, and R_8 are each independently H, methyl or ethyl;

R_3 is *iso*-butyl, toluyl or phenyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is acetyl or benzyloxycarbonyl (Cbz);

Q is -C(O)- or -O-C(O);

R_B is C_{1-4} alkyl or C_{2-4} alkenyl,;

$R_A = -(T)_m-(D)_m-R_1$, in which T is oxygen or carbon, and D is C_{2-4} alkenyl; and

X is a secondary alcohol.

37. The method of any of claims 33-36, wherein:

R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated bond,

R_2, R_4, and R_8 are each independently H, methyl or ethyl;

R_3 is *iso*-butyl, toluyl or phenyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is acetyl or benzyloxycarbonyl (Cbz);

Q is -C(O)- or -O-C(O);

R_8 is C_{1-4} alkyl or C_{2-4} alkenyl,;

R_A = $-(T)_m-(D)_m-R_1$, in which T is oxygen or carbon, and D is C_{2-4} alkenyl.

38. The method of any of claims 33-37, wherein X is $-CH(OH)CF_3$, $-CH(OH)C_2F_5$, $-(CH_2)_rCH(OH)C_kH_{(2k+1-s)}F_s$ in which k is 1-6 and s is 0 to 2k+1, or $-CH(OH)C_6H_{(5-q)}F_q$ in which q is 0 to 5;

the carbon or heterocyclic ring(s) contain from 5-7 members in the ring(s);

r is 0 to 3; and

all alkyl groups contain from 1 to 6 carbon atoms.

39. The method of any of claims 33-38, wherein:

R_8 is H; and

the heterocyclic ring moiety containing R_1 and R_2 and the atoms to which they are attached, is selected from among morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl.

40. The method of any of claims 33-38, wherein:

$(Q)_n$ is a carbonyl group; and

the heterocyclic ring moiety containing R_6 and R_7 and the atoms to which they are attached is selected from among succinimide, phthalimide or maleimide, and is preferably phthalimide.

41. The method of any of claims 33-38, wherein:

n is zero; and

the heterocyclic ring moiety containing R_6 and R_7 and the atoms to which they are attached is morpholino, thiomorpholino, pyrrolidinyl or V-substituted pyrrolidinyl.

42. The method of claim 41, wherein the heterocyclic ring moiety containing R_6 and R_7 is 4-hydroxy pyrrolidinyl or 1,2,3,4-

tetrahydroisoquinoline.

43. The method of any of claims 33-38, wherein:

n is zero; and

R_3 and R_4 or R_6 and R_7 are taken together with the atoms to which they are attached form morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, preferably 4-hydroxy pyrrolidinyl.

44. The method of any of claims 33-38, wherein:

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi) or (vii) as follows:

(i) R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated a double bond, or is cyclic moiety containing from 5 to 6 members;

R_2, R_4, and R_8 are each independently selected from methyl or ethyl or propyl;

R_3 is selected from the group consisting of C_{1-4} alkyl, phenyl, naphthyl, hydroxyphenyl, 1-aminobutyl, acetamide and *iso*-butyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is selected from the group consisting of acetyl, benzyloxycarbonyl (Cbz), 9-fluorenylmethylcarbonate (Fmoc), Ac, BOC and tosyl;

Q is -C(O)-, -S(O)$_2$- or -O-C(O);

R_B is C_{1-4} alkyl or C_{2-4} alkenyl;

$R_A = -(T)_m-(D)_m-R_1$, in which T is oxygen, carbon, or nitrogen, and D is C_{1-4} alkyl or C_{2-4} alkenyl; or

(ii) R_1, R_2, R_3, R_4, R_5, R_8, R_A, Y and R_B are selected as in (i), (iv) or (v);

V is OH or halogen;

n is zero; and

R_6 and R_7 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, 4-hydroxy pyrrolidinyl and 1,2,3,4,tetrahydroisoquinoline; or

(iii) R_1, R_2, R_3, R_4, R_5, R_8, R_A and R_B are selected as in (i);
V is as defined in (ii);
Q is C(O);
n is one; and
R_6 and R_7 together with the atoms to which each is attached form succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_B, Q and n are as defined in any of (i)-(iii) or (v)-(viii),
V is as defined in (ii);
R_8 is H; and
R_1 and R_2 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, R_A, R_B Q and n are as defined in any of (i)-(iv) or (vi)-(viii);
V is as defined in (ii);
R_3 and R_4 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(vi) R_1, R_2, R_3, R_4, R_7, R_8, R_A, R_B, Q and n are as defined in any of (i), (iv) or (v);
V is as defined in (ii);
R_5 and R_6 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6, R_8, R_A and R_B are selected as in (i)

(iv) or (v);

V is as defined in (ii);

n is zero; and

R_5 and R_7 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl.

45. The method of claim 44, wherein at least one of R_1, R_3, and R_5 are selected from the group consisting of C_{2-6} alkenyl and C_{2-6} alkynyl.

46. The method of claim 44 or claim 45, wherein at least one of R_1, R_3, and R_5 are selected from the group consisting of 2-methyl-propene, 2-butene, cyclohexylglycine and cyclohexylalanine.

47. The method of claim 33, wherein the compound is selected from (2*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (1*SR*)-(2*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[1-(thiazole-hexanol)]amide, (2*SR*)-*N*-Cbz-1,1,1-trifluoro-2-heptanol, (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Pro-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-HydroxyPro-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Pro-L-Leu *N*-[3-(1,1,1-trifluoro-2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-HydroxyPro-L-Leu *N*-[3-(1,1,1-trifluoro-2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*SR*)-*N*-valeroyl-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-4-phenyl-2-butanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-4-cyclohexyl-2-butanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-3-phenyl-2-propanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-3-cyclohexyl-2-propanol)]amide, (2*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-butanol)]amide, (3*SR*)-(4S)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(ethyl 2,2-difluoro-3-hydroxyoctanoate)]amide, (4*S*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-octanol)]amide, (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-methyl-3-

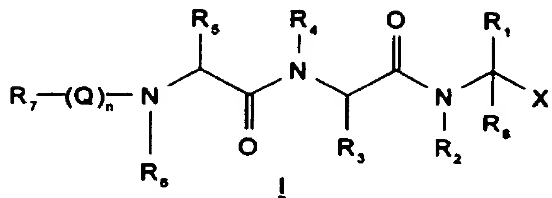
octanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-methyl-2-heptanol)]amide, (2*SR*)-H-L-Leu *N*-[2-(ethyl 4-methyl-4-pentenoate)]amide hydrochloride, (2*SR*)-*N*-[(2*S*)-2-benzoxy-4-methylpentanoyl]-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-Leu *N*-[3-(2-hydroxy-heptanoic acid)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(methyl 2-hydroxy-heptanoate)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(benzyl 2-hydroxy-heptamide)]amide, (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(benzyl 3-hydroxy-octamide)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu N-[3-(1-furfylthio-2-heptanol)]amide, (2*SR*)-*N*-[(2*R*)-[2-(1'-phenyl-1'-propene)-4-methylpentanoyl]]-L-Leu-*N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-*N*-Ac-L-Leu-L-Leu-*N* [2-(trans-4-hexanol)]amide, (2*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, *N*-dansyl-L-Leu-L-Leu-DL-norleucinol, and *N*-Ac-L-Phe-L-Leu-DL-norleucinol.

48. The method of claim 33, wherein the compound is seleted from (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide and (2*SR*)-(3*SR*)-*N*-valeroyl-L-Leu *N*-[3-(1 ,1,1-trifluoro-2-heptanol)]amide.

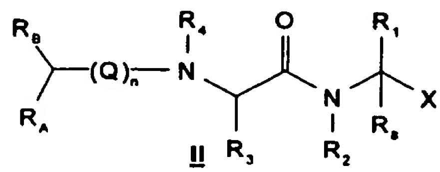
49. The method of claim 33, wherein the disease is selected from the group consisting of Alzheimer's disease, cognition deficits, Downs Syndrome, cerebral hemorrhage with amyloidosis, dementia pugilistica, and head trauma.

50. The method of claim 33, wherein the disease is Alzheimer's disease.

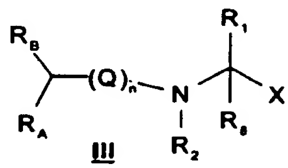
51. A method of treating a patient suffering from a disease characterized by a degradation of the neuronal cytoskeleton resulting from a thrombolytic or hemorrhagic stroke, comprising administering to the patient a therapeutically effective amount of a compound of formula (I), (II) or (III):



I



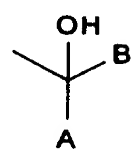
II



III

or the hydrates and isosteres, diastereomeric isomers and mixtures thereof, or pharmaceutically acceptable salts, wherein,

X has the formula:



in which A and B are each independently selected from the group consisting of H, halogen, alkyl, heterocycle, arylalkyl, haloalkyl, in which the alkyl groups are straight or branched chains or form a ring or fused rings,alkylhaloaryl, $(CH_2)_rCHN_2$, $CH_2(CH_2)_rOR_D$, $CH_2(CH_2)_rOZ_D$, $-(CH_2)_{r+1}W$, $-(CH_2)_{r+1}U$, preferably at least one of A or B is H;

r is 0-5;

the alkyl, aryl, carbocyclic and heterocyclic portions of X are unsubstituted or are substituted with one or more substituents independently selected from G;

G is halogen, preferably F, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR';

R and R′ are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3;

the aryl groups preferably contain from 5-6 members and are unsubstituted or substituted with one or more substituents independently selected from G, which is preferably halogen, more preferably fluoro;

the heterocyclic rings preferably contain one or two heteroatoms and preferably contain 5 or 6 members;

Z_D is haloalkyl, in which the alkyl portion is straight or branched, cyclic, or mixtures thereof, the straight or branched chains contain from 1 to about 10, preferably 1-8, more preferably 1-6, most preferably 1-3, carbons in the chain, and the cyclic portions contain from 3 to about 10, preferably 3-7, carbons in the cycle, and the halo portion is preferably fluoro;

U is $-OR_D$ or $-NR_DR_E$;

R_D and R_E are each independently selected from among H, alkyl, preferably lower alkyl, more preferably C_{1-4} alkyl, phenyl, and phenethyl;

W is $-OR_D$, $-SR_D$, and $-NR_DR_E$, or a heterocyclic moiety, preferably containing 4-6, more preferably 5 or 6 members in the ring, and preferably one or two heteroatoms, selected from O, S, or N, in the ring

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi), or (vii) as follows:

(i) R_1, R_3, R_5, and R_8, are each independently selected from a side chain of a naturally occurring α-amino acid, H, alkyl, preferably lower (C_{1-6}) alkyl, alkenyl, preferably C_{2-10} alkenyl, alkynyl, preferably C_{2-6} alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, Y-substituted aryl, aralkyl, aralkenyl, aralkynyl, and Z-substituted heteroaryl, heteroaralkyl, heteroaralkenyl, in which Y is selected from halogen, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR′, R and R′ are independently selected from H or alkyl,

preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3, Z is lower alkyl, preferably C_{1-4} alkyl, or halo lower alkyl, preferably C_{1-4} haloalkyl, more preferably CF_3;

R_2, R_4, R_6, and R_8 are each independently selected from among H and lower alkyl, preferably C_{1-4} alkyl;

R_7 is selected from among C_{1-6} alkyl, aryl, alkenyl, 9-fluoroenyl, aralkyl, aralkenyl, aralkynyl the aryl groups are unsubstituted or are substituted with Z;

Q is selected from among -C(O)-, -O-C(O)-, -C(O)O, $-S(O)_2$- and HN-C(O)-;

n is zero or one;

R_A is $-(T)_m-(D)_m-R_1$ in which T is O or NH, and D is C_{1-4} alkyl or C_{2-4} alkene; and m is zero or one; or

(ii) R_1, R_2, R_3, R_4, R_5, and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH;

n is zero; and

R_6 and R_7 are selected so that with the atoms to which each is attached they form a heterocyclic moiety, which:

(a) contains from 3 to 21 members and one or two or more fused rings, each ring containing preferably 3 to 7, more preferably 4 to 6, members, and is preferably morpholino, thiomorpholino, pyrrolidinyl, V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl, or a reduced isoquinoline, preferably 1,2,3,4,tetrahydroisoquinoline;

(b) does not contain adjacent heteroatoms;

(c) is unsubstituted or substituted with one or more substituents selected from Y, more preferably from V, and

most preferably selected from among OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH; or

(iii) R_1, R_2, R_3, R_4, R_5 and R_8 are selected as in (i);

V is as defined in (ii);

Q is C(O);

n is one; and

R_6 and R_7 are each independently selected as follows:

(a) from carbonyl (C=O), phenyl, a heteroatom, lower alkyl, preferably C_{1-3} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-3} alkyl, and

(b) each is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a cyclic moiety, preferably a 4-6 membered cyclic or 8-12 membered bicylic moiety, and

(d) R_6 and R_7 are selected with the proviso that when two or more heteroatoms are present there is a carbon atom between the heteroatoms; and

(e) the cyclic moiety is preferably succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_B, Q and n are as defined in any of (i)-(iii) or (v)-(vii),

V is as defined in (ii);

R_8 is H; and

R_1 and R_2 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_1 and R_2 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, Q and n are as defined in any of (i)-(iv) or (vi)-(vii);

V is as defined in (ii);

R_3 and R_4 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl;

(vi) R_1, R_2, R_3, R_4, R_7, R_8, Q and n are as defined in any of (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

R_5 and R_6 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_6 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6 and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

n is zero; and

R_5 and R_7 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_7 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl.

52. The method of claim 51, wherein X is selected from $(CH_2)_{r+1}C(OH)$halo-substituted alkyl or $CH(OH)$halo-substituted alkyl, preferably $-CH(OH)C_kH_{(2k+1-s)}F_s$ in which k is 1-6, preferably 1-3, s is 0 to 2k+1; $-CH(OH)C_6H_{(5-q)}F_q$ in which q is 0 to 5; $-(CH_2)_{r+1}C(OH)CF_3$, $-CH(OH)CF_3$, $-(CH_2)_{r+1}C(OH)C_2F_5$, $-CH(OH)C_2F_5$, $-(CH_2)_{r+1}C(OH)H$, $-CH(OH)H$, $-(CH_2)_{r+1}C(OH)(CH_2)_rCHN_2$, $-CH(OH)(CH_2)_rCHN_2$, $-(CH_2)_{r+1}C(OH)$haloalkyl, $-CH(OH)$haloalkyl, $-(CH_2)_{r+1}C(OH)(CH_2)_rU$,

$-CH(OH)(CH_2)_rU$, $-(CH_2)_{r+1}C(OH)CH_2W$ and -CH(OH)haloaryl, and more preferably $-CH(OH)CF_3$ or $-CH(OH)C_2F_5$.

53. The method of claim 51 or claim 52, wherein:

R_1 is H or a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated, preferably a double bond, or is cyclic moiety containing from 5 to 6 members, and is more preferably methyl, 2-methyl propene, 2-butene, cyclohexyl, lower alkyl-substituted cyclohexyl or cyclohexylmethyl, hydroxyphenyl, isopropyl, toluyl, t-butyl, isobutyl, n-butyl, 1-aminobutyl, methylethylthioether and is more preferably n-butyl, toluyl, isobutyl or cyclohexylmethyl;

R_2, R_4 and R_8 are each independently selected from among H or C_{1-4} alkyl, and more preferably methyl or ethyl;

R_3 is H, C_{1-4} alkyl, aryl, particularly phenyl, naphthyl and hydroxyphenyl, 1-aminobutyl, acetamide, and more preferably *iso*-butyl, benzyl, phenyl or toluyl;

R_5 is C_{1-4} alkyl, and more preferably *iso*-butyl;

R_6 is H or C_{1-4} alkyl, and more preferably H or methyl;

R_7 - $(Q)_n$ is acyl (Ac), benzyloxycarbonyl (Cbz), 9-fluorenylmethylcarbonate (Fmoc), BOC, tosyl, with Cbz, Ac and Fmoc being more preferred, and Cbz and Ac most preferred;

Q is -C(O)-, $-S(O)_2$- and -O-C(O)-, with -C(O)- and -O-C(O)- being more preferred, and -O-C(O)- most preferred;

R_B is C_{1-4} alkyl or C_{2-4} alkenyl, and more preferably *iso*-butyl;

R_A is $-(T)_m-(D)_m-R_1$, in which T is oxygen or nitrogen, with oxygen being more preferred, and D is C_{1-4} alkyl or C_{2-4} alkenyl, with a mono-unsaturated C_{3-4} alkenyl being more preferred; and

X, which is as defined above, is preferably a secondary alcohol, and more preferably least one of A or B is H and the other is haloalkyl, in which the carbon chain is straight, branched or cyclic, and is preferably a lower alkyl containing 1-6 carbons, such as CF_3, C_2F_5.

54. The method of any of claims 51-53, wherein:

R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated bond,

R_2, R_4, and R_8 are each independently H, methyl or ethyl;

R_3 is *iso*-butyl, toluyl or phenyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is acetyl or benzyloxycarbonyl (Cbz);

Q is -C(O)- or -O-C(O);

R_B is C_{1-4} alkyl or C_{2-4} alkenyl,;

R_A = $-(T)_m-(D)_m-R_1$, in which T is oxygen or carbon, and D is C_{2-4} alkenyl; and

X is a secondary alcohol.

55. The method of any of claims 51-54, wherein:

R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated bond,

R_2, R_4, and R_8 are each independently H, methyl or ethyl;

R_3 is *iso*-butyl, toluyl or phenyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is acetyl or benzyloxycarbonyl (Cbz);

Q is -C(O)- or -O-C(O);

R_B is C_{1-4} alkyl or C_{2-4} alkenyl,;

R_A = $-(T)_m-(D)_m-R_1$, in which T is oxygen or carbon, and D is C_{2-4} alkenyl.

56. The method of any of claims 51-55, wherein X is $-CH(OH)CF_3$, $-CH(OH)C_2F_5$, $-(CH_2)_rCH(OH)C_kH_{(2k+1-s)}F_s$ in which k is 1-6 and s is 0 to 2k+1, or $-CH(OH)C_6H_{(5-q)}F_q$ in which q is 0 to 5;

the carbon or heterocyclic ring(s) contain from 5-7 members in the ring(s);

r is 0 to 3; and

all alkyl groups contain from 1 to 6 carbon atoms.

57. The method of any of claims 51-56, wherein:

R_8 is H; and

the heterocyclic ring moiety containing R_1 and R_2 and the atoms to which they are attached, is selected from among morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl.

58. The method of any of claims 51-56, wherein:

$(Q)_n$ is a carbonyl group; and

the heterocyclic ring moiety containing R_6 and R_7 and the atoms to which they are attached is selected from among succinimide, phthalimide or maleimide, and is preferably phthalimide.

59. The method of any of claims 51-56, wherein:

n is zero; and

the heterocyclic ring moiety containing R_6 and R_7 and the atoms to which they are attached is morpholino, thiomorpholino, pyrrolidinyl or V-substituted pyrrolidinyl.

60. The method of claim 59, wherein the heterocyclic ring moiety containing R_6 and R_7 is 4-hydroxy pyrrolidinyl or 1,2,3,4-tetrahydroisoquinoline.

61. The method of any of claims 51-56, wherein:

n is zero; and

R_3 and R_4 or R_6 and R_7 are taken together with the atoms to which they are attached form morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, preferably 4-hydroxy pyrrolidinyl.

62. The method of any of claims 51-56, wherein:

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi) or (vii) as follows:

(i) R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated a double bond, or is cyclic

moiety containing from 5 to 6 members;

R_2, R_4, and R_8 are each independently selected from methyl or ethyl or propyl;

R_3 is selected from the group consisting of C_{1-4} alkyl, phenyl, naphthyl, hydroxyphenyl, 1-aminobutyl, acetamide and *iso*-butyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is selected from the group consisting of acetyl, benzyloxycarbonyl (Cbz), 9-fluorenylmethylcarbonate (Fmoc), Ac, BOC and tosyl;

Q is -C(O)-, -$S(O)_2$- or -O-C(O);

R_B is C_{1-4} alkyl or C_{2-4} alkenyl;

R_A = -$(T)_m$-$(D)_m$-R_1, in which T is oxygen, carbon, or nitrogen, and D is C_{1-4} alkyl or C_{2-4} alkenyl; or

(ii) R_1, R_2, R_3, R_4, R_5, R_8, R_A, Y and R_B are selected as in (i), (iv) or (v);

V is OH or halogen;

n is zero; and

R_6 and R_7 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, 4-hydroxy pyrrolidinyl and 1,2,3,4,tetrahydroisoquinoline; or

(iii) R_1, R_2, R_3, R_4, R_5, R_8, R_A and R_B are selected as in (i);

V is as defined in (ii);

Q is C(O);

n is one; and

R_6 and R_7 together with the atoms to which each is attached form succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_B, Q and n are as defined in any

of (i)-(iii) or (v)-(viii),

V is as defined in (ii);

R_8 is H; and

R_1 and R_2 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, R_A, R_B Q and n are as defined in any of (i)-(iv) or (vi)-(viii);

V is as defined in (ii);

R_3 and R_4 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(vi) R_1, R_2, R_3, R_4, R_7, R_8, R_A, R_B, Q and n are as defined in any of (i), (iv) or (v);

V is as defined in (ii);

R_5 and R_6 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6, R_8, R_A and R_B are selected as in (i) (iv) or (v);

V is as defined in (ii);

n is zero; and

R_5 and R_7 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl.

63. The method of claim 62, wherein at least one of R_1, R_3, and R_5 are selected from the group consisting of C_{2-6} alkenyl and C_{2-6} alkynyl.

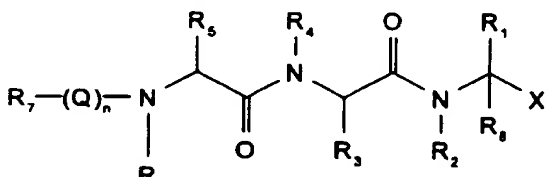
64. The method of claim 62 or claim 63, wherein at least one of R_1, R_3, and R_5 are selected from the group consisting of 2-methyl-propene, 2-butene, cyclohexylglycine and cyclohexylalanine.

65. The method of claim 51, wherein the compound is selected from (2*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (1*SR*)-(2*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[1-(thiazole-hexanol)]amide, (2*SR*)-*N*-Cbz-1,1,1-trifluoro-2-heptanol, (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Pro-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-HydroxyPro-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Pro-L-Leu *N*-[3-(1,1,1-trifluoro-2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-HydroxyPro-L-Leu *N*-[3-(1,1,1-trifluoro-2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*SR*)-*N*-valeroyl-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-4-phenyl-2-butanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-4-cyclohexyl-2-butanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-3-phenyl-2-propanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-3-cyclohexyl-2-propanol)]amide, (2*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-butanol)]amide, (3*SR*)-(4S)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(ethyl 2,2-difluoro-3-hydroxyoctanoate)]amide, (4*S*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-octanol)]amide, (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-methyl-3-octanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-methyl-2-heptanol)]amide, (2*SR*)-H-L-Leu *N*-[2-(ethyl 4-methyl-4-pentenoate)]amide hydrochloride, (2*SR*)-*N*-[(2*S*)-2-benzoxy-4-methylpentanoyl]-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-Leu *N*-[3-(2-hydroxy-heptanoic acid)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(methyl 2-hydroxy-heptanoate)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(benzyl 2-hydroxy-heptamide)]amide, (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(benzyl 3-hydroxy-octamide)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu N-[3-(1-furfylthio-2-heptanol)]amide, (2*SR*)-*N*-[(2*R*)-[2-(1'-phenyl-1'-propene)-4-methylpentanoyl]]-L-Leu-*N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-*N*-Ac-L-Leu-L-Leu-*N* [2-(trans-4-hexanol)]amide,

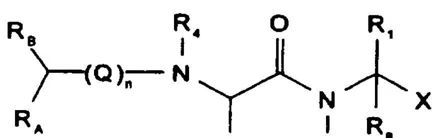
(2*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, *N*-dansyl-L-Leu-L-Leu-DL-norleucinol, and *N*-Ac-L-Phe-L-Leu-DL-norleucinol.

66. The method of claim 51, wherein the compound is seleted from (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide and (2*SR*)-(3*SR*)-*N*-valeroyl-L-Leu *N*-[3-(1 ,1,1-trifluoro-2-heptanol)]amide.

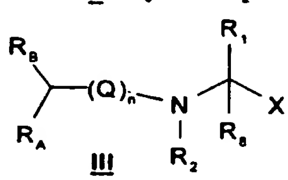
67. A compound having the formula (I), (II) or (III):



I



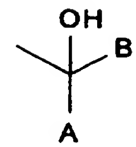
II



III

or the hydrates and isosteres, diastereomeric isomers and mixtures thereof, or pharmaceutically acceptable salts, but with the proviso that: (1) at least one of the amino acid residues in the resulting di or tri-peptide is a non-naturally-occurring α-amino acid or at least one of the R_1, R_3 and R_5 is not a side chain of a naturally-occurring amino acid; and (2) when R_1 is the side chain from a non-naturally occurring amino acid and X is a tertiary or secondary haloalkyl alcohol, R_1 is not the side chain of cyclohexylalanine or cyclohexylglycine, wherein:

X has the formula:



in which A and B are each independently selected from the group consisting of H, halogen, alkyl, heterocycle, arylalkyl, haloalkyl, in which the alkyl groups are straight or branched chains or form a ring or fused rings,alkylhaloaryl, $(CH_2)_rCHN_2$, $CH_2(CH_2)_rOR_D$, $CH_2(CH_2)_rOZ_D$, $-(CH_2)_{r+1}W$, $-(CH_2)_{r+1}U$, preferably at least one of A or B is H;

r is 0-5;

the alkyl, aryl, carbocyclic and heterocyclic portions of X are unsubstituted or are substituted with one or more substituents independently selected from G;

G is halogen, preferably F, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR';

R and R' are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3;

the aryl groups preferably contain from 5-6 members and are unsubstituted or substituted with one or more substituents independently selected from G, which is preferably halogen, more preferably fluoro;

the heterocyclic rings preferably contain one or two heteroatoms and preferably contain 5 or 6 members;

Z_D is haloalkyl, in which the alkyl portion is straight or branched, cyclic, or mixtures thereof, the straight or branched chains contain from 1 to about 10, preferably 1-8, more preferably 1-6, most preferably 1-3, carbons in the chain, and the cyclic portions contain from 3 to about 10, preferably 3-7, carbons in the cycle, and the halo portion is preferably fluoro;

U is $-OR_D$ or $-NR_DR_E$;

R_D and R_E are each independently selected from among H, alkyl, preferably lower alkyl, more preferably C_{1-4} alkyl, phenyl, and phenethyl;

W is $-OR_D$, $-SR_D$, and $-NR_DR_E$, or a heterocyclic moiety, preferably containing 4-6, more preferably 5 or 6 members in the ring, and preferably one or two heteroatoms, selected from O, S, or N, in the ring

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi), or (vii) as follows:

(i) R_1, R_3, R_5, and R_B, are each independently selected from a side chain of a naturally occurring α-amino acid, H, alkyl, preferably lower (C_{1-6}) alkyl, alkenyl, preferably C_{2-10} alkenyl, alkynyl, preferably C_{2-6} alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, Y-substituted aryl, aralkyl, aralkenyl, aralkynyl, and Z-substituted heteroaryl, heteroaralkyl, heteroaralkenyl, in which Y is selected from halogen, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR', R and R' are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3, Z is lower alkyl, preferably C_{1-4} alkyl, or halo lower alkyl, preferably C_{1-4} haloalkyl, more preferably CF_3;

R_2, R_4, R_6, and R_8 are each independently selected from among H and lower alkyl, preferably C_{1-4} alkyl;

R_7 is selected from among C_{1-6} alkyl, aryl, alkenyl, 9-fluoroenyl, aralkyl, aralkenyl, aralkynyl the aryl groups are unsubstituted or are substituted with Z;

Q is selected from among -C(O)-, -O-C(O)-, -C(O)O, $-S(O)_2$- and HN-C(O)-;

n is zero or one;

R_A is $-(T)_m-(D)_m-R_1$ in which T is O or NH, and D is C_{1-4} alkyl or C_{2-4} alkene; and m is zero or one; or

(ii) R_1, R_2, R_3, R_4, R_5, and R_B are selected as in (i),

(iv)(a-c) with R_8 being H or (v)(a-c);

V is OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH;

n is zero; and

R_6 and R_7 are selected so that with the atoms to which each is attached they form a heterocyclic moiety, which:

(a) contains from 3 to 21 members and one or two or more fused rings, each ring containing preferably 3 to 7, more preferably 4 to 6, members, and is preferably morpholino, thiomorpholino, pyrrolidinyl, V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl, or a reduced isoquinoline, preferably 1,2,3,4,tetrahydroisoquinoline;

(b) does not contain adjacent heteroatoms;

(c) is unsubstituted or substituted with one or more substituents selected from Y, more preferably from V, and most preferably selected from among OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH; or

(iii) R_1, R_2, R_3, R_4, R_5 and R_8 are selected as in (i);

V is as defined in (ii);

Q is C(O);

n is one; and

R_6 and R_7 are each independently selected as follows:

(a) from carbonyl (C=O), phenyl, a heteroatom, lower alkyl, preferably C_{1-3} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-3} alkyl, and

(b) each is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are

attached form a cyclic moiety, preferably a 4-6 membered cyclic or 8-12 membered bicylic moiety, and

(d) R_6 and R_7 are selected with the proviso that when two or more heteroatoms are present there is a carbon atom between the heteroatoms; and

(e) the cyclic moiety is preferably succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_B, Q and n are as defined in any of (i)-(iii) or (v)-(vii),

V is as defined in (ii);

R_8 is H; and

R_1 and R_2 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_1 and R_2 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, Q and n are as defined in any of (i)-(iv) or (vi)-(vii);

V is as defined in (ii);

R_3 and R_4 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present,

there is at least one carbon atom between each heteroatom, and

(b) is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl;

(vi) R_1, R_2, R_3, R_4, R_7, R_8, Q and n are as defined in any of (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

R_5 and R_6 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_6 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6 and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

n is zero; and

R_5 and R_7 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom,

with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_7 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl.

68. The compound of claim 67, wherein X is selected from the group consisting of $(CH_2)_{r+1}C(OH)$halo-substituted alkyl or CH(OH)halo-substituted alkyl, preferably $-CH(OH)C_kH_{(2k+1-s)}F_s$ in which k is 1-6, preferably 1-3, s is 0 to 2k+1; $-CH(OH)C_6H_{(5-q)}F_q$ in which q is 0 to 5; $-(CH_2)_{r+1}C(OH)CF_3$, $-CH(OH)CF_3$, $-(CH_2)_{r+1}C(OH)C_2F_5$, $-CH(OH)C_2F_5$, $-(CH_2)_{r+1}C(OH)H$, -CH(OH)H, $-(CH_2)_{r+1}C(OH)(CH_2)_rCHN_2$, $-CH(OH)(CH_2)_rCHN_2$, $-(CH_2)_{r+1}C(OH)$haloalkyl, -CH(OH)haloalkyl, $-(CH_2)_{r+1}C(OH)(CH_2)_rU$, $-CH(OH)(CH_2)_rU$, $-(CH_2)_{r+1}C(OH)CH_2W$ and -CH(OH)haloaryl, and more preferably $-CH(OH)CF_3$ or $-CH(OH)C_2F_5$.

69. The compound of claim 67 or 68, wherein:

R_1 is H or a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated, preferably a double bond, or is cyclic moiety containing from 5 to 6 members, and is more preferably methyl, 2-methyl propene, 2-butene, cyclohexyl, lower alkyl-substituted cyclohexyl or cyclohexylmethyl, hydroxyphenyl, isopropyl, toluyl, t-butyl, isobutyl, n-butyl, 1-aminobutyl, methylethylthioether and is more preferably n-butyl, toluyl, isobutyl or cyclohexylmethyl;

R_2, R_4 and R_8 are each independently selected from among H or C_{1-4} alkyl, and more preferably methyl or ethyl;

R_3 is H, C_{1-4} alkyl, aryl, particularly phenyl, naphthyl and hydroxyphenyl, 1-aminobutyl, acetamide, and more preferably *iso*-butyl,

benzyl, phenyl or toluyl;

R_5 is C_{1-4} alkyl, and more preferably *iso*-butyl;

R_6 is H or C_{1-4} alkyl, and more preferably H or methyl;

R_7 - $(Q)_n$ is acyl (Ac), benzyloxycarbonyl (Cbz), 9-fluorenylmethylcarbonate (Fmoc), BOC, tosyl, with Cbz, Ac and Fmoc being more preferred, and Cbz and Ac most preferred;

Q is -C(O)-, $-S(O)_2-$ and -O-C(O)-, with -C(O)- and -O-C(O)- being more preferred, and -O-C(O)- most preferred;

R_8 is C_{1-4} alkyl or C_{2-4} alkenyl, and more preferably *iso*-butyl;

R_A is $-(T)_m-(D)_m-R_1$, in which T is oxygen or nitrogen, with oxygen being more preferred, and D is C_{1-4} alkyl or C_{2-4} alkenyl, with a mono-unsaturated C_{3-4} alkenyl being more preferred; and

X, which is as defined above, is preferably a secondary alcohol, and more preferably least one of A or B is H and the other is haloalkyl, in which the carbon chain is straight, branched or cyclic, and is preferably a lower alkyl containing 1-6 carbons, such as CF_3, C_2F_5.

70. The compound of any of claims 67-69, wherein:

R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated bond,

R_2, R_4, and R_8 are each independently H, methyl or ethyl;

R_3 is *iso*-butyl, toluyl or phenyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is acetyl or benzyloxycarbonyl (Cbz);

Q is -C(O)- or -O-C(O);

R_8 is C_{1-4} alkyl or C_{2-4} alkenyl,;

$R_A = -(T)_m-(D)_m-R_1$, in which T is oxygen or carbon, and D is C_{2-4} alkenyl; and

X is a secondary alcohol.

71. The compound of any of claims 67-70, wherein:

R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated bond,

R_2, R_4, and R_8 are each independently H, methyl or ethyl;

R_3 is *iso*-butyl, toluyl or phenyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is acetyl or benzyloxycarbonyl (Cbz);

Q is -C(O)- or -O-C(O);

R_B is C_{1-4} alkyl or C_{2-4} alkenyl,;

R_A = $-(T)_m-(D)_m-R_1$, in which T is oxygen or carbon, and D is C_{2-4} alkenyl.

72. The compound of any of claims 67-71, wherein X is $-CH(OH)CF_3$, $-CH(OH)C_2F_5$, $-(CH_2)_rCH(OH)C_kH_{(2k+1-s)}F_s$ in which k is 1-6 and s is 0 to 2k + 1, or $-CH(OH)C_6H_{(5-q)}F_q$ in which q is 0 to 5;

the carbon or heterocyclic ring(s) contain from 5-7 members in the ring(s);

r is 0 to 3; and

all alkyl groups contain from 1 to 6 carbon atoms.

73. The compound of any of claims 67-72, wherein:

R_8 is H; and

the heterocyclic ring moiety containing R_1 and R_2 and the atoms to which they are attached, is selected from among morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl.

74. The compound of any of claims 67-72, wherein:

$(Q)_n$ is a carbonyl group; and

the heterocyclic ring moiety containing R_6 and R_7 and the atoms to which they are attached is selected from among succinimide, phthalimide or maleimide, and is preferably phthalimide.

75. The compound of any of claims 67-72, wherein:

n is zero; and

the heterocyclic ring moiety containing R_6 and R_7 and the atoms to which they are attached is morpholino, thiomorpholino, pyrrolidinyl or V-substituted pyrrolidinyl.

76. The compound of claim 75, wherein the heterocyclic ring moiety containing R_6 and R_7 is 4-hydroxy pyrrolidinyl or 1,2,3,4-tetrahydroisoquinoline.

77. The compound of any of claims 67-72, wherein:

n is zero; and

R_3 and R_4 or R_5 and R_7 are taken together with the atoms to which they are attached form morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, preferably 4-hydroxy pyrrolidinyl.

78. The compound of any of claims 67-72, wherein:

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi) or (vii) as follows:

(i) R_1 is a straight or branched chain carbon chain containing 2 to 6 carbons and one unsaturated a double bond, or is cyclic moiety containing from 5 to 6 members;

R_2, R_4, and R_8 are each independently selected from methyl or ethyl or propyl;

R_3 is selected from the group consisting of C_{1-4} alkyl, phenyl, naphthyl, hydroxyphenyl, 1-aminobutyl, acetamide and *iso*-butyl;

R_5 is C_{1-4} alkyl;

R_6 is H or C_{1-4} alkyl;

R_7 - $(Q)_n$ is selected from the group consisting of acetyl, benzyloxycarbonyl (Cbz), 9-fluorenylmethylcarbonate (Fmoc), Ac, BOC and tosyl;

Q is -C(O)-, -S(O)$_2$- or -O-C(O);

R_B is C_{1-4} alkyl or C_{2-4} alkenyl;

R_A = $-(T)_m-(D)_m-R_1$, in which T is oxygen, carbon, or

nitrogen, and D is C_{1-4} alkyl or C_{2-4} alkenyl; or

(ii) R_1, R_2, R_3, R_4, R_5, R_8, R_A, Y and R_B are selected as in (i), (iv) or (v);

V is OH or halogen;

n is zero; and

R_6 and R_7 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, 4-hydroxy pyrrolidinyl and 1,2,3,4,tetrahydroisoquinoline; or

(iii) R_1, R_2, R_3, R_4, R_5, R_8, R_A and R_B are selected as in (i);

V is as defined in (ii);

Q is C(O);

n is one; and

R_6 and R_7 together with the atoms to which each is attached form succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_B, Q and n are as defined in any of (i)-(iii) or (v)-(viii),

V is as defined in (ii);

R_8 is H; and

R_1 and R_2 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, R_A, R_B Q and n are as defined in any of (i)-(iv) or (vi)-(viii);

V is as defined in (ii);

R_3 and R_4 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(vi) R_1, R_2, R_3, R_4, R_7, R_8, R_A, R_B, Q and n are as defined in any of (i), (iv) or (v);

V is as defined in (ii);

R_5 and R_6 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6, R_8, R_A and R_B are selected as in (i) (iv) or (v);

V is as defined in (ii);

n is zero; and

R_5 and R_7 together with the atoms to which each is attached form a moiety selected from the group consisting of morpholino, thiomorpholino, pyrrolidinyl, and 4-hydroxy pyrrolidinyl.

79. The compound of claim 78, wherein at least one of R_1, R_3, and R_5 are selected from the group consisting of C_{2-6} alkenyl and C_{2-6} alkynyl.

80. The compound of claim 78 or claim 79, wherein at least one of R_1, R_3, and R_5 are selected from the group consisting of 2-methyl-propene, 2-butene, cyclohexylglycine and cyclohexylalanine.

81. The compound of claim 67, wherein the compound is selected from (2*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (1*SR*)-(2*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[1-(thiazole-hexanol)]amide, (2*SR*)-*N*-Cbz-1,1,1-trifluoro-2-heptanol, (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Pro-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-HydroxyPro-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Pro-L-Leu *N*-[3-(1,1,1-trifluoro-2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-HydroxyPro-L-Leu *N*-[3-(1,1,1-trifluoro-2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*SR*)-*N*-valeroyl-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-4-phenyl-2-butanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-4-cyclohexyl-2-butanol)]amide, (3*SR*)-*N*-Cbz-L-

Leu-L-Leu *N*-[3-(1,1,1-trifluoro-3-phenyl-2-propanol)]amide, (3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-3-cyclohexyl-2-propanol)]amide, (2*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-butanol)]amide, (3*SR*)-(4S)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(ethyl 2,2-difluoro-3-hydroxyoctanoate)]amide, (4*S*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-octanol)]amide, (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(1,1,1-trifluoro-2,2-difluoro-3-methyl-3-octanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-methyl-2-heptanol)]amide, (2*SR*)-H-L-Leu *N*-[2-(ethyl 4-methyl-4-pentenoate)]amide hydrochloride, (2*SR*)-*N*-[(2*S*)-2-benzoxy-4-methylpentanoyl]-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-Leu *N*-[3-(2-hydroxy-heptanoic acid)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(methyl 2-hydroxy-heptanoate)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[3-(benzyl 2-hydroxy-heptamide)]amide, (3*SR*)-(4*S*)-*N*-Cbz-L-Leu-L-Leu *N*-[4-(benzyl 3-hydroxy-octamide)]amide, (2*SR*)-(3*S*)-*N*-Cbz-L-Leu-L-Leu N-[3-(1-furfylthio-2-heptanol)]amide, (2*SR*)-*N*-[(2*R*)-[2-(1'-phenyl-1'-propene)-4-methylpentanoyl]]-L-Leu-*N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-*N*-Ac-L-Leu-L-Leu-*N* [2-(trans-4-hexanol)]amide, (2*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, (2*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[2-(4-methyl-4-pentenol)]amide, *N*-dansyl-L-Leu-L-Leu-DL-norleucinol, and *N*-Ac-L-Phe-L-Leu-DL-norleucinol.

82. The compound of claim 67, wherein the compound is seleted from (2*SR*)-(3*SR*)-*N*-Ac-L-Leu-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide, (2*SR*)-(3*SR*)-*N*-Cbz-L-Leu *N*-[3-(1,1,1-trifluoro-2-heptanol)]amide and (2*SR*)-(3*SR*)-*N*-valeroyl-L-Leu *N*-[3-(1 ,1,1-trifluoro-2-heptanol)]amide.

83. Use of a compound of any of claims 67-82 for the manufacture of a medicament for treating a neurodegenerative disease that is characterized by the deposition of cerebral amyloid.

84. Use of a compound of any of claims 67-82 for the manufacture of a medicament for treating a disease characterized by a degradation of the neuronal cytoskeleton resulting from a thrombolytic or hemorrhagic stroke.

85. An article of manufacture, comprising packaging material and a compound of any of claims 67-82 contained within the packaging material, wherein the compound is effective for treating a neurodegenerative disease that is characterized by the deposition of cerebral amyloid; and the packaging material includes a label that indicates that the compound or salt thereof is used for treating a neurodegenerative disease that is characterized by the deposition of cerebral amyloid.

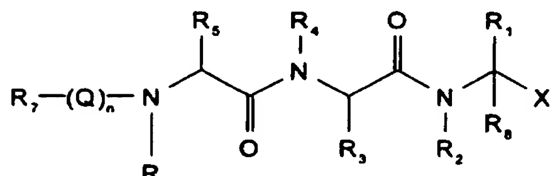
86. An article of manufacture, comprising packaging material and a compound of any of claims 67-82 contained within the packaging material, wherein the compound is effective for treating a disease characterized by a degradation of the neuronal cytoskeleton resulting from a thrombolytic or hemorrhagic stroke; and the packaging material includes a label that indicates that the compound or salt thereof is used for treating a disease characterized by a degradation of the neuronal cytoskeleton resulting from a thrombolytic or hemorrhagic stroke.

87. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of claim 67 in a physiologically acceptable carrier.

88. A pharmaceutical composition formulated for single dosage administration, comprising, in a physiologically acceptable carrier, a therapeutically effective amount of a compound of claim 67.

89. A combination, comprising:

(A) a composition, comprising an effective amount of a compound of formula (I), (II) or (III):



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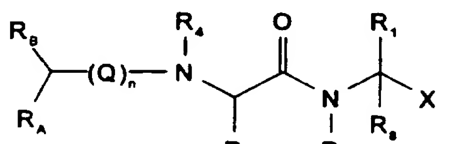

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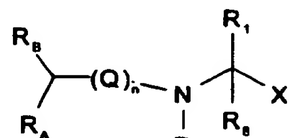
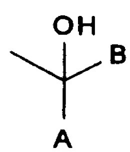


III

or the hydrates and isosteres, diastereomeric isomers and mixtures thereof, or pharmaceutically acceptable salts, wherein:

X has the formula:



in which A and B are each independently selected from the group consisting of H, halogen, alkyl, heterocycle, arylalkyl, haloalkyl, in which the alkyl groups are straight or branched chains or form a ring or fused rings,alkylhaloaryl, $(CH_2)_rCHN_2$, $CH_2(CH_2)_rOR_D$, $CH_2(CH_2)_rOZ_D$, $-(CH_2)_{r+1}W$, $-(CH_2)_{r+1}U$, preferably at least one of A or B is H;

r is 0-5;

the alkyl, aryl, carbocyclic and heterocyclic portions of X are unsubstituted or are substituted with one or more substituents independently selected from G;

G is halogen, preferably F, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR';

R and R' are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3;

the aryl groups preferably contain from 5-6 members and are unsubstituted or substituted with one or more substituents independently selected from G, which is preferably halogen, more preferably fluoro;

the heterocyclic rings preferably contain one or two heteroatoms and preferably contain 5 or 6 members;

Z_D is haloalkyl, in which the alkyl portion is straight or branched, cyclic, or mixtures thereof, the straight or branched chains contain from 1 to about 10, preferably 1-8, more preferably 1-6, most preferably 1-3, carbons in the chain, and the cyclic portions contain from 3 to about 10, preferably 3-7, carbons in the cycle, and the halo portion is preferably fluoro;

U is $-OR_D$ or $-NR_DR_E$;

R_D and R_E are each independently selected from among H, alkyl, preferably lower alkyl, more preferably C_{1-4} alkyl, phenyl, and phenethyl;

W is $-OR_D$, $-SR_D$, and $-NR_DR_E$, or a heterocyclic moiety, preferably containing 4-6, more preferably 5 or 6 members in the ring, and preferably one or two heteroatoms, selected from O, S, or N, in the ring

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi), or (vii) as follows:

(i) R_1, R_3, R_5, and R_B, are each independently selected from a side chain of a naturally occurring α-amino acid, H, alkyl, preferably lower (C_{1-6}) alkyl, alkenyl, preferably C_{2-10} alkenyl, alkynyl, preferably C_{2-6} alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl,

heteroaralkyl, heteroaralkenyl, Y-substituted aryl, aralkyl, aralkenyl, aralkynyl, and Z-substituted heteroaryl, heteroaralkyl, heteroaralkenyl, in which Y is selected from halogen, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR', R and R' are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3, Z is lower alkyl, preferably C_{1-4} alkyl, or halo lower alkyl, preferably C_{1-4} haloalkyl, more preferably CF_3;

R_2, R_4, R_6, and R_8 are each independently selected from among H and lower alkyl, preferably C_{1-4} alkyl;

R_7 is selected from among C_{1-6} alkyl, aryl, alkenyl, 9-fluoroenyl, aralkyl, aralkenyl, aralkynyl the aryl groups are unsubstituted or are substituted with Z;

Q is selected from among -C(O)-, -O-C(O)-, -C(O)O, —$S(O)_2$- and HN-C(O)-;

n is zero or one;

R_A is -$(T)_m$-$(D)_m$-R_1 in which T is O or NH, and D is C_{1-4} alkyl or C_{2-4} alkene; and m is zero or one; or

(ii) R_1, R_2, R_3, R_4, R_5, and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH;

n is zero; and

R_6 and R_7 are selected so that with the atoms to which each is attached they form a heterocyclic moiety, which:

(a) contains from 3 to 21 members and one or two or more fused rings, each ring containing preferably 3 to 7, more preferably 4 to 6, members, and is preferably morpholino, thiomorpholino, pyrrolidinyl, V-substituted pyrrolidinyl,

particularly 4-hydroxy pyrrolidinyl, or a reduced isoquinoline, preferably 1,2,3,4,tetrahydroisoquinoline;

(b) does not contain adjacent heteroatoms;

(c) is unsubstituted or substituted with one or more substituents selected from Y, more preferably from V, and most preferably selected from among OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH; or

(iii) R_1, R_2, R_3, R_4, R_5 and R_8 are selected as in (i);

V is as defined in (ii);

Q is C(O);

n is one; and

R_6 and R_7 are each independently selected as follows:

(a) from carbonyl (C=O), phenyl, a heteroatom, lower alkyl, preferably C_{1-3} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-3} alkyl, and

(b) each is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a cyclic moiety, preferably a 4-6 membered cyclic or 8-12 membered bicylic moiety, and

(d) R_6 and R_7 are selected with the proviso that when two or more heteroatoms are present there is a carbon atom between the heteroatoms; and

(e) the cyclic moiety is preferably succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_8, Q and n are as defined in any of (i)-(iii) or (v)-(vii),

V is as defined in (ii);

R_8 is H; and

R_1 and R_2 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_1 and R_2 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, Q and n are as defined in any of (i)-(iv) or (vi)-(vii);

V is as defined in (ii);

R_3 and R_4 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl;

(vi) R_1, R_2, R_3, R_4, R_7, R_8, Q and n are as defined in any of (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

R_5 and R_6 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_6 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6 and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

n is zero; and

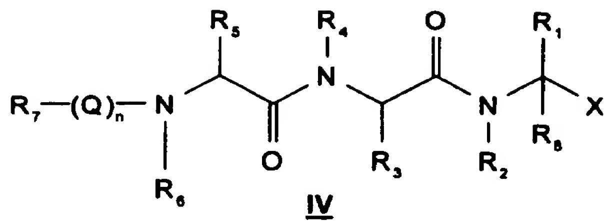
R_5 and R_7 are each independently selected as follows:

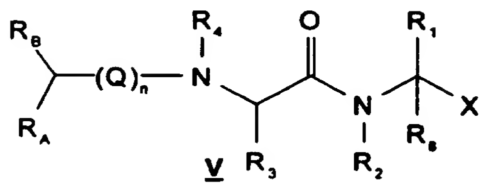
(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_7 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; and

(B) a composition, comprising an effective amount of a compound having formula (IV) or (V):





or the hydrates and isosteres, diastereomeric isomers and mixtures thereof, or pharmaceutically acceptable salts thereof, wherein:

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, X, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi) or (vii) as follows:

(i) R_1, R_3, R_5, and R_B, are each independently selected from a side chain of a naturally occurring α-amino acid, H, alkyl, preferably lower (C_{1-6}) alkyl, alkenyl, preferably C_{2-10} alkenyl, alkynyl, preferably C_{2-6} alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, Y-substituted aryl, aralkyl, aralkenyl, aralkynyl, and Z-substituted heteroaryl, heteroaralkyl, heteroaralkenyl, in which Y is selected from halogen, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR', R and R' are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3, Z is lower alkyl, preferably C_{1-4} alkyl, or halo lower alkyl, preferably C_{1-4} haloalkyl, more preferably CF_3;

R_2, R_4, R_6, and R_8 are each independently selected from among H and lower alkyl, preferably C_{1-4} alkyl;

R_7 is selected from among C_{1-6} alkyl, aryl, alkenyl, 9-fluoroenyl, aralkyl, aralkenyl, aralkynyl the aryl groups are

unsubstituted or are substituted with Z;

Q is selected from among -C(O)-, -O-C(O)-, -C(O)O-, $-S(O)_2$- and HN-C(O)-;

n is zero or one;

R_A is $-(T)_m-(D)_m-R_1$ in which T is O or NH, and D is C_{1-4} alkyl or C_{2-4} alkene; and m is zero or one;

X is selected from $-(CH_2)_rC(O)H$, $-(CH_2)_rC(O)$haloalkyl, $-(CH_2)_rC(O)(CH_2)_rCHN_2$, $-C(CH_2)_r(O)C(CH_2)_r(O)OR_D$, $-(CH_2)_rC(O)(CH_2)_rC(O)NR_DR_E$, $-(CH_2)_rC\equiv N$, $-(CH_2)_rC(OH)(CH_2)_rC(O)U$, $-(CH_2)_rC(OH)CH_2C(O)U$, $-(CH_2)_rC(O)W$ and $-(CH_2)_rC(O)CH_2W$, in which: R_D and R_E are independently selected from among H, alkyl, preferably lower alkyl, more preferably C_{1-4} alkyl, phenyl, benzyl, and phenethyl; U is $-OR_D$ or $-NR_DR_E$, and W is $-OR_D$, $-SR_D$, and $-NR_DR_E$, or heterocyclic moiety, preferably containing 4-6, more preferably 5 or 6 members in the ring, and preferably one or two heteroatoms, selected from O, S, or N, in the ring, and r is 0-5, preferably 0-3, more preferably 0 or 1, most preferably 0; or

(ii) R_1, R_2, R_3, R_4, R_5, R_8, and X are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH;

n is zero; and

R_6 and R_7 are selected so that with the atoms to which each is attached they form a heterocyclic moiety, which:

(a) contains from 3 to 21 members and one or two or more fused rings, each ring containing preferably 3 to 7, more preferably 4 to 6, members, and is preferably morpholino, thiomorpholino, pyrrolidinyl, V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl, or a reduced isoquinoline,

preferably 1,2,3,4,tetrahydroisoquinoline;

(b) does not contain adjacent heteroatoms;

(c) is unsubstituted or substituted with one or more substituents selected from Y, more preferably from V, and most preferably selected from among OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH; or

(iii) R_1, R_2, R_3, R_4, R_5, R_8, and X are selected as in (i);

V is as defined in (ii);

Q is C(O);

n is one; and

R_6 and R_7 are each independently selected as follows:

(a) from carbonyl (C=O), phenyl, a heteroatom, lower alkyl, preferably C_{1-3} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-3} alkyl, and

(b) each is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a cyclic moiety, preferably a 4-6 membered cyclic or 8-12 membered bicylic moiety, and

(d) R_6 and R_7 are selected with the proviso that when two or more heteroatoms are present there is a carbon atom between the heteroatoms; and

(e) the cyclic moiety is preferably succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_B, Q, X and n are as defined in any of (i)-(iii) or (v)-(vii),

V is as defined in (ii);

R_8 is H; and

R_1 and R_2 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_1 and R_2 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, R_A, R_B, X, Q and n are as defined in any of (i)-(iv) or (vi)-(vii);

V is as defined in (ii);

R_3 and R_4 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl;

(vi) R_1, R_2, R_3, R_4, R_7, R_8, Q, X and n are as defined in any of (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

R_5 and R_6 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_6 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6, R_8, and X are selected as in (i) (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

n is zero; and

R_5 and R_7 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_7 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; and

wherein the amounts of each composition are effective for inhibiting one or more proteases or for treating a neurodegenerative

disease that is characterized by the deposition of cerebral amyloid when compositions (A) and (B) are used in combination.

90. The combination of claim 89, wherein compositions (A) and (B) are mixed to form a composition.

91. A method of treating a neurodegenerative disease that is characterized by the deposition of cerebral amyloid, comprising administering to a subject an effective amount of the combination of claim 89, wherein:

compositions (A) and (B) are administered simultaneously, successively or intermittently; and

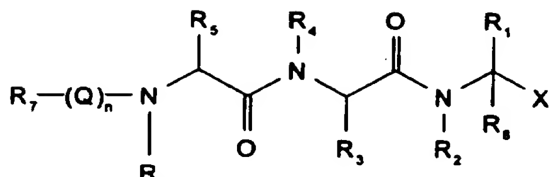
the amount is effective when compositions (A) and (B) are used in combination.

92. Use of the combination of claim 89 for manufacture of a medicament for the treatment of a neurodegenerative disease that is characterized by the deposition of cerebral amyloid

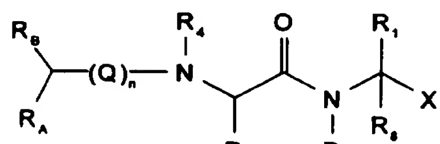
93. A method of inhibiting one or more proteases, comprising contacting cells with a protease inhibiting amount of the combination of claim 89, wherein cells are contacted with (A) and (B) simultaneously, successively or intermittently.

94. A kit, comprising

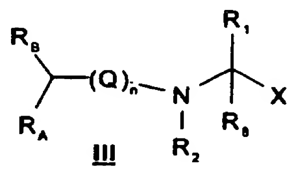
(A) a first composition, containing an effective amount of a compound of formula (I), (II) or (III):



I



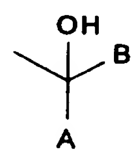
II



III

or the hydrates and isosteres, diastereomeric isomers and mixtures thereof, or pharmaceutically acceptable salts, wherein:

X has the formula:



in which A and B are each independently selected from the group consisting of H, halogen, alkyl, heterocycle, arylalkyl, haloalkyl, in which the alkyl groups are straight or branched chains or form a ring or fused rings,alkylhaloaryl, $(CH_2)_rCHN_2$, $CH_2(CH_2)_rOR_D$, $CH_2(CH_2)_rOZ_D$, $-(CH_2)_{r+1}W$, $-(CH_2)_{r+1}U$, preferably at least one of A or B is H;

r is 0-5;

the alkyl, aryl, carbocyclic and heterocyclic portions of X are unsubstituted or are substituted with one or more substituents independently selected from G;

G is halogen, preferably F, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR';

R and R′ are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3;

the aryl groups preferably contain from 5-6 members and are unsubstituted or substituted with one or more substituents independently selected from G, which is preferably halogen, more preferably fluoro;

the heterocyclic rings preferably contain one or two heteroatoms and preferably contain 5 or 6 members;

Z_D is haloalkyl, in which the alkyl portion is straight or branched, cyclic, or mixtures thereof, the straight or branched chains contain from 1 to about 10, preferably 1-8, more preferably 1-6, most preferably 1-3, carbons in the chain, and the cyclic portions contain from 3 to about 10, preferably 3-7, carbons in the cycle, and the halo portion is preferably fluoro;

U is $-OR_D$ or $-NR_DR_E$;

R_D and R_E are each independently selected from among H, alkyl, preferably lower alkyl, more preferably C_{1-4} alkyl, phenyl, and phenethyl;

W is $-OR_D$, $-SR_D$, and $-NR_DR_E$, or a heterocyclic moiety, preferably containing 4-6, more preferably 5 or 6 members in the ring, and preferably one or two heteroatoms, selected from O, S, or N, in the ring

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi), or (vii) as follows:

(i) R_1, R_3, R_5, and R_8, are each independently selected from a side chain of a naturally occurring α-amino acid, H, alkyl, preferably lower (C_{1-6}) alkyl, alkenyl, preferably C_{2-10} alkenyl, alkynyl, preferably C_{2-6} alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, Y-substituted aryl, aralkyl, aralkenyl, aralkynyl, and Z-substituted heteroaryl, heteroaralkyl, heteroaralkenyl, in which Y is selected from halogen, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR′, R and R′ are independently selected from H or alkyl,

preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3. Z is lower alkyl, preferably C_{1-4} alkyl, or halo lower alkyl, preferably C_{1-4} haloalkyl, more preferably CF_3;

R_2, R_4, R_6, and R_8 are each independently selected from among H and lower alkyl, preferably C_{1-4} alkyl;

R_7 is selected from among C_{1-6} alkyl, aryl, alkenyl, 9-fluoroenyl, aralkyl, aralkenyl, aralkynyl the aryl groups are unsubstituted or are substituted with Z;

Q is selected from among -C(O)-, -O-C(O)-, -C(O)O, $-S(O)_2$- and HN-C(O)-;

n is zero or one;

R_A is $-(T)_m-(D)_m-R_1$ in which T is O or NH, and D is C_{1-4} alkyl or C_{2-4} alkene; and m is zero or one; or

(ii) R_1, R_2, R_3, R_4, R_5, and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH;

n is zero; and

R_6 and R_7 are selected so that with the atoms to which each is attached they form a heterocyclic moiety, which:

(a) contains from 3 to 21 members and one or two or more fused rings, each ring containing preferably 3 to 7, more preferably 4 to 6, members, and is preferably morpholino, thiomorpholino, pyrrolidinyl, V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl, or a reduced isoquinoline, preferably 1,2,3,4,tetrahydroisoquinoline;

(b) does not contain adjacent heteroatoms;

(c) is unsubstituted or substituted with one or more substituents selected from Y, more preferably from V, and

most preferably selected from among OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH; or

(iii) R_1, R_2, R_3, R_4, R_5 and R_8 are selected as in (i);
V is as defined in (ii);
Q is C(O);
n is one; and
R_6 and R_7 are each independently selected as follows:

(a) from carbonyl (C=O), phenyl, a heteroatom, lower alkyl, preferably C_{1-3} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-3} alkyl, and

(b) each is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a cyclic moiety, preferably a 4-6 membered cyclic or 8-12 membered bicylic moiety, and

(d) R_6 and R_7 are selected with the proviso that when two or more heteroatoms are present there is a carbon atom between the heteroatoms; and

(e) the cyclic moiety is preferably succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_B, Q and n are as defined in any of (i)-(iii) or (v)-(vii),
V is as defined in (ii);
R_8 is H; and
R_1 and R_2 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_1 and R_2 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, Q and n are as defined in any of (i)-(iv) or (vi)-(vii);

V is as defined in (ii);

R_3 and R_4 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl;

(vi) R_1, R_2, R_3, R_4, R_7, R_8, Q and n are as defined in any of (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

R_5 and R_6 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_6 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6 and R_8 are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

n is zero; and

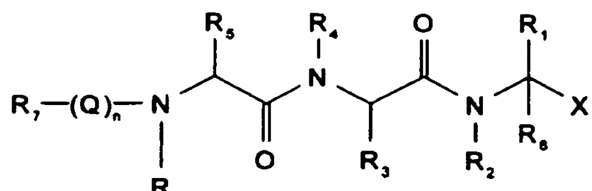
R_5 and R_7 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

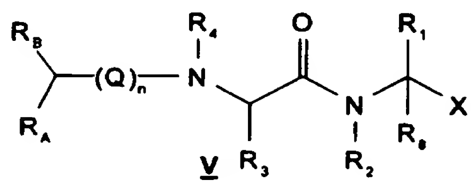
(b) R_5 and R_7 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; and

(B) a second composition, comprising an effective amount of a compound having formula (IV) or (V):



IV



V

or the hydrates and isosteres, diastereomeric isomers and mixtures thereof, or pharmaceutically acceptable salts thereof, wherein:

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, X, Q and n are selected from among (i), (ii), (iii), (iv), (v), (vi) or (vii) as follows:

(i) R_1, R_3, R_5, and R_B, are each independently selected from a side chain of a naturally occurring α-amino acid, H, alkyl, preferably lower (C_{1-6}) alkyl, alkenyl, preferably C_{2-10} alkenyl, alkynyl, preferably C_{2-6} alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, Y-substituted aryl, aralkyl, aralkenyl, aralkynyl, and Z-substituted heteroaryl, heteroaralkyl; heteroaralkenyl, in which Y is selected from halogen, lower alkyl, alkoxy, OH, haloalkyl, preferably CF_3, NO_2, nitrile, S-alkyl, phenyl, and -NRR', R and R' are independently selected from H or alkyl, preferably lower alkyl, OH and halo-lower alkyl, particularly CF_3, Z is lower alkyl, preferably C_{1-4} alkyl, or halo lower alkyl, preferably C_{1-4} haloalkyl, more preferably CF_3;

R_2, R_4, R_6, and R_8 are each independently selected from among H and lower alkyl, preferably C_{1-4} alkyl;

R_7 is selected from among C_{1-6} alkyl, aryl, alkenyl, 9-fluoroenyl, aralkyl, aralkenyl, aralkynyl the aryl groups are

unsubstituted or are substituted with Z;

Q is selected from among -C(O)-, -O-C(O)-, -C(O)O-, $-S(O)_2$- and HN-C(O)-;

n is zero or one;

R_A is -$(T)_m$-$(D)_m$-R_1 in which T is O or NH, and D is C_{1-4} alkyl or C_{2-4} alkene; and m is zero or one;

X is selected from -$(CH_2)_r$C(O)H, -$(CH_2)_r$C(O)haloalkyl, -$(CH_2)_r$C(O)$(CH_2)_r$$CHN_2$, -C$(CH_2)_r$(O)C$(CH_2)_r(O)OR_D$, -$(CH_2)_r$C(O)$(CH_2)_r$C(O)NR_DR_E, -$(CH_2)_r$C≡N, -$(CH_2)_r$C(OH)$(CH_2)_r$C(O)U, -$(CH_2)_r$C(OH)CH_2C(O)U, -$(CH_2)_r$C(O)W and -$(CH_2)_r$C(O)CH_2W, in which: R_D and R_E are independently selected from among H, alkyl, preferably lower alkyl, more preferably C_{1-4} alkyl, phenyl, benzyl, and phenethyl; U is -OR_D or -NR_DR_E, and W is -OR_D, -SR_D, and -NR_DR_E, or heterocyclic moiety, preferably containing 4-6, more preferably 5 or 6 members in the ring, and preferably one or two heteroatoms, selected from O, S, or N, in the ring, and r is 0-5, preferably 0-3, more preferably 0 or 1, most preferably 0; or

(ii) R_1, R_2, R_3, R_4, R_5, R_8, and X are selected as in (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH;

n is zero; and

R_6 and R_7 are selected so that with the atoms to which each is attached they form a heterocyclic moiety, which:

(a) contains from 3 to 21 members and one or two or more fused rings, each ring containing preferably 3 to 7, more preferably 4 to 6, members, and is preferably morpholino, thiomorpholino, pyrrolidinyl, V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl, or a reduced isoquinoline,

preferably 1,2,3,4,tetrahydroisoquinoline;

(b) does not contain adjacent heteroatoms;

(c) is unsubstituted or substituted with one or more substituents selected from Y, more preferably from V, and most preferably selected from among OH, halogen, lower alkyl, preferably methyl or ethyl or halogen-substituted lower alkyl, preferably methyl or ethyl, and is preferably OH; or

(iii) R_1, R_2, R_3, R_4, R_5, R_8, and X are selected as in (i);

V is as defined in (ii);

Q is C(O);

n is one; and

R_6 and R_7 are each independently selected as follows:

(a) from carbonyl (C=O), phenyl, a heteroatom, lower alkyl, preferably C_{1-3} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-3} alkyl, and

(b) each is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a cyclic moiety, preferably a 4-6 membered cyclic or 8-12 membered bicylic moiety, and

(d) R_6 and R_7 are selected with the proviso that when two or more heteroatoms are present there is a carbon atom between the heteroatoms; and

(e) the cyclic moiety is preferably succinimide, phthalimide or maleimide; or

(iv) R_3, R_4, R_5, R_6, R_7, R_A, R_8, Q, X and n are as defined in any of (i)-(iii) or (v)-(vii),

V is as defined in (ii);

R_8 is H; and

R_1 and R_2 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_1 and R_2 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(v) R_1, R_2, R_5, R_6, R_7, R_8, R_A, R_B, X, Q and n are as defined in any of (i)-(iv) or (vi)-(vii);

V is as defined in (ii);

R_3 and R_4 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) is unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl;

(vi) R_1, R_2, R_3, R_4, R_7, R_8, Q, X and n are as defined in any of (i), (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

R_5 and R_6 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_6 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; or

(vii) R_1, R_2, R_3, R_4, R_6, R_8, and X are selected as in (i) (iv)(a-c) with R_8 being H or (v)(a-c);

V is as defined in (ii);

n is zero; and

R_5 and R_7 are each independently selected as follows:

(a) from lower alkyl, preferably C_{1-4} alkyl, or lower alkyl linked to a heteroatom, preferably C_{1-4} alkyl, or a heteroatom, with the proviso that when more than one heteroatom is present, there is at least one carbon atom between each heteroatom, and

(b) R_5 and R_7 are unsubstituted or substituted with Y, preferably with V, and

(c) together with the atoms to which they are attached form a heterocyclic moiety, preferably a 4-6 membered heterocyclic moiety, that is preferably morpholino, thiomorpholino, pyrrolidinyl, or V-substituted pyrrolidinyl, particularly 4-hydroxy pyrrolidinyl; and

wherein the amounts of the compounds of formula (I), (II) or (III) and the compounds of formula (IV) or (V) are effective, when used in combination, for inhibiting one or more proteases or for treating a

a neurodegenerative disease that is characterized by the deposition of cerebral amyloid; and the compositions are formulated for single dosage use.

95. A compound of claim 1, wherein:

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_A, R_B, Q, n and X are as defined above for formulae (I), (II) and (III), but in which either R_7-$(Q)_n$ in formula (I) and R_8-$CH(R_A)$-$(Q)_n$ in formulae (II) and (III) or X is replaced with a chemical labeling/linker group or a chromophore or a fluorophore useful for identifying and/or isolating proteases.

96. The compound of claim 95, wherein X is replaced with a chromophore or fluorophore selected from among *p*-nitroanilide, 4-methoxy-β-naphthylamide, or 7-amino-4-methylcoumarin.

97. The compound of claim 95, wherein the R_7-$(Q)_n$ moiety and the (R_B)-$CH(R_A)$-$(Q)_n$ moiety are chemical labeling/linking groups that permit detection and/or isolation of the peptide to which they are coupled.

98. The compound of claim 97, wherein the R_7-$(Q)_n$ moiety and the (R_B)-$CH(R_A)$-$(Q)_n$ moiety are selected from among biotin, radiolabeled moieties, fluorescein, and primary amines.

99. The compound of claim 98, wherein the amines are 6-amino caproic acid and amino decanoic acid.

AN 125:196393 MARPAT

TI Preparation of peptide, peptide analog and amino acid analog as protease inhibitors

IN Munoz, Benito; Mcdonald, Ian Alexander; Albrecht, Elisabeth

PA The Salk Institute Biotechnology/industrial Associ, USA

SO PCT Int. Appl., 217 pp.
CODEN: PIXXD2

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DS W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN

AI 96WO-US00360 960105

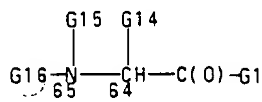
PRAI 95US-0369422 950106
95US-0403420 950313

DT Patent

LA English

AB The title compds. represented by formulas $R^7-(Q)_n-NR^6CHR^5CONR^4CHR^3CONR^2CR^1R^8X$ (I), $R^BR^ACH-(Q)_n-NR^4CHR^3CONR^2CR^1R^8X$ (II), and $R^BR^ACH-(Q)_n-NR^2CR^1R^8X$ (III) [R^1 is preferably 2-Me propene, 2-butene, norleucine; R^2, R^4, and R^8 are each independently Me or ethyl; R^3 is preferably iso-Bu or phenyl; R^5 is preferably isobutyl; R^6 is H or methyl; $R^7-(Q)_n$ is preferably benzyloxycarbonyl or acetyl; Q is preferably CO; R^B is preferably iso-butyl; R^A = $(T)_m-(D)_m-R^1$, in which T is preferably oxygen or carbon, and D is preferably a mono-unsatd. C_{3-4} alkenyl; X is an alc., particularly a secondary alc.], useful as protease inhibitors (no data), are prepd. A method for inhibiting a protease comprises contacting cells with a protease-inhibiting amt. of the compd. I, II, or III. A method for (1) treating a neurodegenerative disease (e.g. Alzheimer's disease, cognition deficits, Downs Syndrome, cerebral hemorrhage with amyloidosis, dementia pugilistica, and head trauma) characterized by the cerebral deposition of amyloid and (2) treating a patient suffering from a disease characterized by a degrdn. of the neuronal cytoskeleton resulting from a thrombolytic or hemorrhagic stroke comprises administering to the patient a therapeutically effective amt. of the compd. I, II, or III. Thus, Z-Leu-Leu-OH was condensed with Et 2-amino-4-methyl-4-pentenoate hydrochloride (prepn. given) using HOBT, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and Et_3N in CH_2Cl_2 to give 47.3% Z-Leu-Leu-$NHCH(CO_2Et)CH_2CMe:CH_2$ as a mixt. of diastereomers, which was reduced by $LiBH_4$ in EtOAc at 0° for 30 min to give 85.6% Z-Leu-Leu-$NHCH(CH_2OH)CH_2CMe:CH_2$ as a mixt. of diastereomers.

MSTR 1



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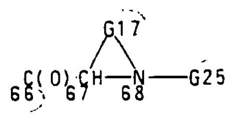

G17 = R
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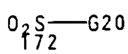

DER: or pharmaceutically acceptable salts or hydrates
MPL: claim 89
NTE: substitution is restricted
STE: or isoteres, diastereomeric isomers and mixtures